A compound of formula (I) for medicinal use: R₁, R₂, R₃, R⁴ and R⁵ independently represent hydrogen, halogen, -SO₃H, -S(O)₂NR₅R⁶, -NR₅S(O)₂R₆, -NR₅-C(O)R₆, -NR₅-C(O)-NR₅, -NR₅-C(O)-N-, -OR₅, -NHC(O)R₅ or -N(C(O)R₅); R⁶ and R⁷ independently represent a hydrogen, fluoro or Cl-C₆H₄-Cl or Cl-C₆H₄-Cl; R₈ and R⁹ independently represent hydrogen or Cl-C₆H₄-Cl; R₁₀ and R₁₁ independently represent hydrogen or Cl-C₆H₄-Cl; B is -C(O)R₅-C(R)=C(R₅)R₁₀ or C(R)=C(R₅)R₁₀; and when A is -C₆H₄-Cl, B may additionally be -OCR₅R₆, -NR₅-C(O)R₆ or -SO₃H-R₅. W is Cl-C₆H₄-Cl optionally substituted by one or more substituents independently selected from fluoro, ary1, heteroary1 or Cl-C₆H₄-Cl, the latter group being optionally substituted by one or more fluoro atoms; and n is 0, 1 or 2.
QUINOLINE DERIVATIVES HAVING DP AND/OR CRTH2 RECEPTOR ACTIVITY

Field of the Invention

This invention relates to a class of quinoline compounds which are ligands of the DP receptor and of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on TH1 Helper cells type 2), and their use in the treatment of diseases responsive to modulation of DP and/or 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 of the Invention

Mast cells are known to play an important role in allergic and immune responses through the release of a number of mediators, such as histamine, leukotrienes, cytokines, prostaglandin D₂, etc (Boyce; Allergy Asthma Proα, 2004, 25, 27-30). Prostaglandin D₂ (PGD₂) is the major cyclooxygenase metabolite of arachidonic acid produced by mast cells in response to allergen challenge (Lewis et al; J. Immunol., 1982, 129, 1627-1631). It has been shown that PGD₂ production is increased in patients with systemic mastocytosis (Roberts; N. Engl. J. Med., 1980, 303, 1400-1404), allergic rhinitis (Naclerio et al; Am. Rev. Respir. Dis., 1983, 128, 597-602; Brown et al; Arch. Otolarynol.


Transgenic mice lacking the DP receptor have been shown to produce lower concentrations of Th2 cytokines and reduced accumulation of eosinophils and lymphocytes in the bronchial alveolar lavage fluid compared to wild-type mice after antigen challenge (Matsuoka et al; Science, 2000, 287, 2013-2017). Furthermore, the DP receptor-deficient mice exhibited much reduced airway sensitivity to acetylcholine after antigen challenge when compared to wild type mice. In addition, the DP receptor antagonist molecule S-5751 (Mitsumori et al; J. Med. Chem., 2003, 46, 2436-2445) has been shown to inhibit both early (as...
assessed by sneezing, mucosal plasma exudation and nasal blockage) and late
(as assessed by eosinophil infiltration) phase nasal responses in a guinea pig
asthma model after oral dosing (Arimura et al., J. Pharmacol. Exp. Ther., 2001,
298, 411-419). Furthermore, S-5751 alleviated allergen-induced plasma
exudation in the conjunctiva in an allergic conjunctivitis model and antigen-
induced eosinophil infiltration into the lung in a guinea pig asthma model.
Genetic variants with impaired expression of the DP receptor gene are linked to
reduced asthma risk (Lilly et al., Am. J. Respir. Cell Mol. Biol., 2005, 33, 224-
226).

The CRTH2 receptor has been shown to be expressed on cell types
associated with allergic inflammation, such as basophils, eosinophils, and Th2-
type immune helper cells (Hirai et al., J. Exp. Med., 2001, 193, 255-261). The
CRTH2 receptor has been shown to mediate PGD2-mediated cell migration in
these cell types (Hirai et al.; J. Exp. Med., 2001, 193, 255-261), and also to play
a major role in neutrophil and eosinophil cell recruitment in a model of contact
dermatitis (Takeshita et al., Int. Immunol., 2004, 16, 947-959). Ramatroban ((3R)-
S-^florophenylSulphonylamino-l ^S^-tetrahydro- 9H-carbazole-9-propanoic
acid), a dual CRTH2 and thromboxane A2 receptor antagonist, has been shown
to attenuate these responses (Sugimoto et al., J. Pharmacol. Exp. Ther, 2003,
305, 347-352; Takeshita et al, op. cit). In addition, exogenously administered
CRTH2 agonists enhance the allergic response in sensitised mice (Spik et al., J.
Immunol., 2005, 174, 3703-3708). In rats exogenously applied CRTH2 agonists
cause a pulmonary eosinophilia (Shirashi et al, J. Pharmacol. Exp Ther., 2005,
312, 954-960).

These observations suggest the DP and CRTH2 receptors may function
independently to regulate aspects of allergic inflammation. Therefore, it is
expected that small molecules antagonists of DP and/or CRTH2 receptors may
be useful in the treatment and/or prevention of diseases mediate by PGD2; for
example, asthma and allergic diseases.

A number of DP antagonists have been described. For example, S-5751,
described above, and related compounds based around bicycloheptanyl and
oxabicycloheptanyl cores have been described as DP receptor antagonists, and,
in some cases, as mixed PGD2 receptor and thromboxane (TXA2 or TP) receptor
WO2001/094309; WO2000/053573; WO1 999/1 5502; WO1 998/2591 5;


The quinoline template is a common one in compounds proposed for use as pharmaceuticals. However the compounds with which the present invention is concerned have a substitution pattern on the quinoline template which distinguishes them from specific known quinoline-type pharmaceuticals or known generally proposed classes of quinoline-type pharmaceuticals.

**Summary of the invention**

One aspect of the invention provides quinoline derivatives of formula (I) for medicinal use:
R₁, R₂, R₃, R₄ and R₅ independently represent hydrogen, halogen, 
-S(O)ₙ R₆, -S(O)₂ NR₇ R₈, -NR₇(S(O))₂ R₆, -NR₇ COR₆, -CONR₇ R₈, -COR₆, 
-NO₂, -CN, -OR₇, C₅ C₆alkyl or C₃-C₇cycloalkyl, the latter two groups being 
optionally substituted by one or more fluoro atoms;
R₆ is CrC₆alkyl or C₃-C₇cycloalkyl, optionally substituted by one or more 
fluoro atoms;
R₇ and R₈ independently represent hydrogen, C₅ C₆alkyl or 
C₃-C₇cycloalkyl, the latter two groups being optionally substituted by one or more 
fluoro atoms; 
A is -0-, -S(O)ₙ, -CR⁹R¹₀, -NR¹¹ or -C(O);
R⁹ and R¹₀ independently represent a hydrogen, fluoro or C₅ C₆alkyl;
R¹¹ and R¹² independently represent hydrogen or CrC₆alkyl;
B is -C(R⁹R¹₀JC(R⁹R¹₀)- or C(R¹¹)=C(R¹²);
when A is -CR⁹R¹₀, B may additionally be -OCR⁹R¹₀, -NR¹¹CR⁹R¹₀ and 
-S(O)ₙ CR⁹R¹₀;
W is CrC₆alkyl optionally substituted by one or more substituents 
independently selected from fluoro, aryl, heteroaryl or C₃-C₇cycloalkyl, the latter 
group being optionally substituted with one or more fluoro atoms; and 
X is a carboxylic acid group, a tetrazolyl group, or a group of formula 
-CONHS(O)₂ R¹₃ or -S(O)₂ NHCOR¹₃;
R¹₃ is aryl, heteroaryl, CrC₆alkyl or C₃-C₇cycloalkyl, the latter two groups 
being optionally substituted by one or more fluoro atoms;
n is 0, 1 or 2.
Medicinal use of compounds of the invention includes use in therapy.
The series of compounds defined by formula (I) above is believed to be novel, except for the specific compounds referred to in Examples 1-10 herein, which are currently commercially available but for which no medicinal use has been proposed. The invention therefore in includes compounds of formula (I) *per se*, with the exception of those of Examples 1-10 herein.

Compounds of formula (I) above may be prepared or recovered in the form of salts, N-oxides, hydrates, and solvates thereof. Any reference herein, including the claims herein, to "compounds of the invention", "compounds with which the invention is concerned" or "compounds of formula (I)" and the like, includes reference to salts, particularly pharmaceutically acceptable salts, N-oxides, hydrates, and solvates of such compounds.

Compounds with which the invention is concerned are DP and/or CRTH2 receptor antagonists.

The invention also includes (i) use of a compound with which the invention is concerned in the manufacture of a medicament for use in the treatment of conditions responsive to modulation of DP and/or CRTH2 receptor activity, and (ii) a method of treatment of conditions responsive to modulation of DP and/or CRTH2 receptor activity, comprising administering to a patient suffering such disease an effective amount of a compound with which the invention is concerned.

Examples of conditions responsive to modulation of DP and CRTH2 receptor activity include asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer’s lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer’s disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington’s disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneuropathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet’s Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter’s syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren’s Syndrome, soft tissue disease,
Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephrititic 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 of asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome, or allergic rhinobronchitis. Psoriasis, atopic and non-atopic dermatitis Crohn's disease, ulcerative colitis, and irritable bowel disease are other specific conditions where the present compounds may have particular utility.

Another aspect of the invention is a pharmaceutical composition comprising a compound with which the invention is concerned in admixture with a pharmaceutically acceptable carrier or excipient.

Terminology

As used herein, the term "(C\textsubscript{a}-C\textsubscript{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, /7-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, f-butyl, n-pentyl and n-hexyl.

As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-6 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. Aryl radicals may have, for example, from 6 to 14 ring carbon atoms, preferably from 6 to 10 carbon atoms. Illustrative of aryl radicals are phenyl, biphenyl and naphtyl.

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 thiethyl, benzthienyl, furyl,
benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl and indazolyl.

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, for example sodium and potassium hydroxides; alkaline earth metal hydroxides, for example calcium, barium and magnesium hydroxides; with organic bases, for example N-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, N-ethyl piperidine, dibenzylamine and the like. Specific salts with bases include the benzathine, calcium, diolamine, meglumine, olamine, potassium, procaine, sodium, tromethamine and zinc salts. Those compounds of the invention which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, for example with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids, for example acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, p-toluenesulphonic, benzoic, benzenesulphonic, glutamic, lactic and mandelic acids and the like. Where a compound contains a quaternary ammonium group acceptable counter-ions may be, for example chlorides, bromides, sulfates, methanesulfonates, benzenesulfonates, toluenesulfonates (tosylates), napadisylates (naphthalene-1,5-disulfonates or naphthalene-1-(sulfonic acid)-5-sulfonates), edisylates (ethane-1,2-disulfonates or ethane-1-(sulfonic acid)-2-sulfonates), isethionates (2-hydroxyethylsulfonates), phosphates, acetates, citrates, lactates, tartrates, mesylates, maleates, malates, fumarates, succinates, xinafoates, p-acetamidobenzoates and the like; wherein the number of quaternary ammonium species balances the pharmaceutically acceptable salt such that the compound has no net charge.


The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or
more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Compounds with which the invention is concerned may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, and in such cases can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomers 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 with which the invention is concerned is also part of the invention. "Prodrug" means a compound which is convertible in vivo by metabolic means (for example, by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of formula (I) are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-p-toluyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, p-toluenesulphonates, cyclohexylsulphamates and quinates. Examples of ester prodrugs are those described by F. J. Leinweber, Drug Metab. Res., 1987, 18, 379. As used in herein, references to the compounds of formula (I) are meant to also include the prodrug forms.

Structural aspects of compounds with which the invention is concerned

Radical A is -O-, -S(O)$_n$ -CR$_{12}$ R$_{13}$ or -NR$_8$ wherein

R$_9$ represents hydrogen,

 Ci-C$_6$ alkyl such as methyl, ethyl, or n- or isoo-propyl, or
 C$_3$-C$_7$ cycloalkyl such as cyclopropyl, cyclopentyl or cyclohexyl, and
 R$_{12}$ and R$_{13}$ independently represent hydrogen,

halogen such as fluoro or chloro,

 Ci-C$_6$ alkyl such as methyl or ethyl, or
 C$_3$-C$_7$ cycloalkyl such as cyclopropyl, cyclopentyl or cyclohexyl, the latter two C$_1$-C$_6$ alkyl and C$_3$-C$_7$ cycloalky groups being optionally substituted with one or more substituents independently
selected from halogen such as fluoro, C₃-C₇ cycloalkyl such as cyclopropyl,
-NR₉R₁₀ or -OR₉ wherein
R₉ is as defined and discussed above, and

R¹⁰ represents hydrogen, C₁-C₆ alkyl such as methyl, ethyl, or n- or iso-propyl, or C₃-C₇ cycloalkyl such as cyclopropyl, cyclopentyl or cyclohexyl;
or R₁² and R₁³ when attached to the same carbon atom may form a 3-8 membered ring optionally containing one or more atoms selected from O, S, -NR₁⁴ and itself optionally substituted by one or more C₁-C₃ alkyl or halogen atoms.
R¹⁴ may be hydrogen, C₁-C₆ alkyl such as methyl, C₃-C₇ cycloalkyl such as cyclopropyl, -SO₂R₁¹ or -C(O)C₁-C₄ alkyl such as methyl-, ethyl- or n- or iso-propyl-carbonyl.
R¹¹ may be C₁-C₆ alkyl such as methyl or ethyl, or C₃-C₇ cycloalkyl such as cyclopropyl, and R¹¹ may be optionally substituted with one or more halogen atoms such as fluorine; Examples of rings formed by R₁² and R₁³ when attached to the same carbon atom include cyclopropyl, cyclopentyl, cyclohexyl, piperidinyl, and /V-(C₁-C₆ alkyl) piperidinyl.

Currently it is preferred that the radical A be -S-.

B is -C(R₁²R₁³JC(R₁²R₁³))- or C(R₁⁵)=C(R₁⁶) wherein R₁² and R₁³ are as defined and discussed in relation to radical A above, and R₁⁵ and R₁⁶ independently represent hydrogen or C₁-C₆ alkyl such as methyl or ethyl. Currently preferred are the cases where, in radical B, R₁², R₁³, R₁⁵ and R₁⁶ are each hydrogen.

W is CrC₆ alkyl such as methyl, ethyl, n- or iso-propyl, n-, sec- or tert-butyl, or n-pentyl, optionally substituted by one or more substituents independently selected from halogen such as fluoro or chloro, aryl such as phenyl, heteroaryl such as pyridyl, pyrimidinyl, thienyl, thiazolyl, or imidazolyl, -OR₉, -NR₉R₁⁰, -S(O)₉R₁¹,
-CONR₉R₁⁰, -NR₉COR₁⁰, -SO₂R₉R₁⁰, -NR₉S(O)₂R₁¹ wherein R₉, R₁⁰, and R₁¹ are as defined and discussed above in connection with radical A, or
C₃–C₇ cycloalkyl such as cyclopropyl, cyclopentyl or cyclohexyl, the latter group being optionally substituted with one or more halogen atoms; and

X = is a carboxylic acid group, a tetrazolyl group, or a group of formula -CONHS(O)₂R₆ or -S(O)₂NHCOR₆ wherein R₆ is aryl such as phenyl, heteroaryl, such as pyridyl, C₆R₃ alkyl such as methyl ethyl, n- or iso-propyl, or n-sec- or tert-butyl, or C₃–C₇ cycloalkyl such as cyclopropyl, cyclopentyl or cyclohexyl, the latter two C₆R₃ alkyl and C₃–C₇ cycloalkyl groups being optionally substituted by one or more halogen atoms.

Compositions

As mentioned above, the compounds with which the invention is concerned are DP and/or CRTH2 receptor antagonists, 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 bronchitis.

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. In general, the daily dose range will lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, often 0.01 mg to about 50 mg per kg, for example 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. 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; tableting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants
for example potato starch, or acceptable wetting agents such as sodium lauryl sulfate. 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.

The drug may also be formulated for inhalation, for example as a nasal spray, or dry powder or aerosol inhalers. For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation. Aerosol generation can be carried out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronized active compounds from, for example, inhalation capsules or other "dry powder" delivery systems.

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.

Other compounds may be combined with compounds with which the invention is concerned for the prevention and treatment of prosta
glandin-mediated diseases. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating PGD2-mediated
diseases comprising a therapeutically effective amount of a compound of the invention and one or more other therapeutic agents. Suitable therapeutic agents for a combination therapy with compounds of the invention include, but are not limited to: (1) corticosteroids, such as fluticasone, ciclesonide or budesonide; (2) β2-adrenoreceptor agonists, such as salmeterol, indacaterol or formoterol; (3) leukotriene modulators, for example leukotriene antagonists such as montelukast, zafirulast or pranlukast or leukotriene biosynthesis inhibitors such as Zileuton or BAY-1005; (4) anticholinergic agents, for example muscarinic-3 (M3) receptor antagonists such as tiotropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, such as roflumilast or cilomilast; (6) antihistamines, for example selective histamine-1 (H1) receptor antagonists, such as fexofenadine, cetirizine, loratidine or astemizole; (7) antitussive agents, such as codeine or dextromorphan; (8) non-selective COX-1 / COX-2 inhibitors, such as ibuprofen or ketoprofen; (9) COX-2 inhibitors, such as celecoxib and rofecoxib; (10) VLA-4 antagonists, such as those described in WO97/03094 and WO97/02289; (11) TACE inhibitors and TNF-α inhibitors, for example anti-TNF monoclonal antibodies, such as Remicade and CDP-870 and TNF receptor immunoglobulin molecules, such as Enbrel; (12) inhibitors of matrix metalloprotease, for example MMP12; (13) human neutrophil elastase inhibitors, such as those described in WO2005/026124, WO2003/053930 and WO06/082412; (14) A2a agonists such as those described in EP1 052264 and EP1241 176 (15) A2b antagonists such as those described in WO2002/42298; (16) modulators of chemokine receptor function, for example antagonists of CCR3 and CCR8; (17) compounds which modulate the action of other prostanoid receptors, for example a thromboxane A₂ antagonist; and (18) agents that modulate Th2 function, such as PPAR agonists.

The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

**Synthesis**

There are multiple synthetic strategies for the synthesis of the compounds with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds of the invention can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature

It may be necessary to protect reactive functional groups (for example, hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of formula (I) to avoid their unwanted participation in a reaction leading to the formation of compounds of formula (I). Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 1999, may be used.

The compounds of the invention of formula (I) may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free acid form corresponding to isolated salts can be generated by acidification with a suitable acid such as acetic acid and hydrochloric acid and extraction of the liberated free acid into an organic solvent followed by evaporation. The free acid form isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate base and subsequent evaporation, precipitation, or crystallisation.

Compounds of the invention are accessible by the routes shown in Schemes 1 to 8. Compounds of the invention of formula (Ia) may conveniently be prepared by the reaction between a compound of formula (II) and a suitable alkylation agent of formula [III], where group LG represents a suitable leaving group (for example, chloro, bromo, or methanesulfonyloxy) and E is a hydrogen or alkyl group. Typically, the alkylation reaction is carried out in the presence of a base (for example, potassium carbonate or sodium hydride) in an inert solvent (for example, tetrahydrofuran or N,N-dimethylformamide). It is to be understood that if the reaction is carried out on a protected form of (III) an appropriate deprotection step will be required to obtain the desired compound of the invention (Ia) (Scheme 1).
Intermediate compounds of formula (II) may conveniently be prepared by the reaction between an aniline of formula (IV) and a β-ketoester of formula (V), in which PG represents an appropriate ester function (for example, methyl or ethyl) (Scheme 2). The reaction may be carried out neat or in the presence of a suitable dehydrating agent, such as polyphosphoric acid, p-toluenesulfonic acid or methanesulfonic acid. Intermediate compounds of formula (IV) and (V) are known or may be prepared from known compounds according to methods known to those skilled in the art.

Compounds of the invention of formula (Ib) are accessible from intermediate compounds of formula (VI) by alkylation in a similar manner to that used for the preparation of compounds of formula (Ia) from compounds of formula (II) (Scheme 3).
Intermediate compounds of formula (VI) may in turn be prepared from compounds of formula (II) by treatment with Lawesson's reagent \([2,4\text{-bis}(4\text{-methoxyphenyl})\text{-}2,4\text{-dithiooxo-}1,3,2,4\text{-dithiadiphosphetane}]\) (Scheme 4). The reaction is typically carried out at 80 to 120°C, in a suitable solvent, such as benzene or toluene.

Alternatively, compounds of the invention of formula (Ib) may be prepared from intermediate compounds of formula (VII) by reaction with a thiol of formula (VIII) in the presence of a suitable base such as potassium carbonate (Scheme 5). It is to be understood that if the reaction is carried out on a protected form of thiol (VIII) an appropriate deprotection step will be required to obtain the desired compound of the invention (Ib).
Compounds of the invention of formula (VII) may be conveniently prepared from compounds of formula (II), by treatment with phosphorus oxychloride or thionyl chloride (Scheme 6). Thiols of formula (VIII) are known or may be prepared from known compounds according to methods known to those skilled in the art.

![Scheme 6](image)

Compounds of the invention of formula (Ic) may be conveniently prepared from compounds of formula (VII), by reaction with an amine of formula (IX). The reaction is typically carried out in a polar aprotic solvent, such as acetonitrile or \(\Lambda,\Lambda\)-dimethylformamide at a temperature between 80 and 120 °C. Alternatively, the reaction may be carried out in the presence of a suitable catalyst [for example, palladium (II) acetate / 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene] and a base (for example, triethylamine) (Scheme 7). It is to be understood that if the reaction is carried out on a protected form of intermediate (IX) an appropriate deprotection step will be required to obtain the desired compound of the invention (Ic).

![Scheme 7](image)

It will be understood by those practiced in the art that compounds of the invention may be prepared by transformations of other compounds of the invention. For example, compounds of the invention of formula (Id) may be prepared by the oxidation of compounds of the invention of formula (Ib), with a
suitable oxidising agent such as potassium peroxymonosulfate, meta-chloroperoxybenzoic acid or other well known oxidising agents (Scheme 8).

Examples

$^1$H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5 mm probe spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br = broad singlet, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet. Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 µm 100 x 3.0 mm column and a 2 mL/minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 2 minutes.

Example 1: 3-(6-methoxy-2-methyl-3-propylquinolin-4-ylsulfanyl)propionic acid (CAS No. 333424-02-5)
\[ \text{H NMR (DMSO-}d_6\text{): } \delta \ 0.97 \ (t, J = 7.5 \text{ Hz, } 3\text{H}), \ 1.48 \ (m, 2\text{H}), \ 2.39 \ (t, J = 6.8 \text{ Hz, } 2\text{H}), \ 2.62 \ (s, 3\text{H}), \ 2.96 \ (t, J = 6.8 \text{ Hz, } 2\text{H}), \ 3.02 \ (m, 2\text{H}), \ 3.89 \ (s, 3\text{H}), \ 7.29 \ (dd, J = 2.8, 9.1 \text{ Hz, } 1\text{H}), \ 7.68 \ (d, J = 2.8 \text{ Hz, } 1\text{H}), \ 7.80 \ (d, J = 9.1 \text{ Hz, } 1\text{H}), \ 12.35 \ (br \ s, 1\text{H}). \]

MS: ESI (⁺ve): 320 (M+H)⁺, Retention time 8.6 min.

Example 2: 3-(2,6-dimethyl-3-propylquinolin-4-ylsulfanyl)propionic acid (CAS No. 333424-00-3)

Example 3: 3-(2,8-dimethyl-3-propylquinolin-4-ylsulfanyl)propionic acid (CAS No. 333424-01-4)

Example 4: 3-(6-bromo-2-methyl-3-propylquinolin-4-ylsulfanyl)propionic acid (CAS No. 370848-98-9)
Example 5: 3-(3-butyl-2,8-dimethylquinolin-4-ylsulfanyl)propionic acid (CAS No. 370851-71-1)

Example 6: 3-(3-butyl-2-methylquinolin-4-ylsulfanyl)propionic acid (CAS No. 333424-04-7)

Example 7: 3-(2-methyl-3-propylquinolin-4-ylsulfanyl)propionic acid (CAS No. 383896-42-2)
Example 8: 3-(3-butyl-6-methoxy-2-methylquinolin-4-ylsulfanyl)propionic acid (CAS No. 378779-71-6)

Example 9: 3-(3-butyl-2,6-dimethylquinolin-4-ylsulfanyl)propionic acid (CAS No. 370855-40-6)

Example 10: 3-(6-bromo-3-butyl-2-methylquinolin-4-ylsulfanyl)propionic acid (CAS No. 369392-97-2)

Biological Methods

Compounds of the invention were tested using the following biological test methods to determine their ability to displace PGD$_2$ from the DP and CRTH2 receptors.

DP Radioligand Binding Assay

The receptor binding assay is performed in a final volume of 200 µl binding buffer (10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01% BSA) using 1 nM [$^3$H]-PGD$_2$ (Amersham Biosciences UK Ltd) as the
radioligand. Ligands are added in assay buffer containing a constant volume of DMSO (1% by volume). Total binding is determined using 1% by volume of DMSO in assay buffer and non-specific binding is determined using 10 μM of unlabeled PGD₂ (Sigma). The reaction is initiated with 100 μg LS174T cell membranes, and the mixture incubated for 90 minutes at room temperature.

The reaction is terminated by rapid filtration through GF/C filters prewetted with brij 35 (1% by volume) using a Packard Cell harvester and the filter washed with 600 μL/well of wash buffer (10 mM BES pH 7.4 and 120 mM NaCl). The residual radioligand bound to the filter is determined using a Topcount liquid scintillation counter (Perkin Elmer). Compound IC₅₀ value was determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC₅₀ calculations were performed using Excel and XL fit (Microsoft) and this value is used to determine a Kᵢ value for the test compound using the Cheng-Prusoff equation.

**CRTH2 Radioligand Binding Assay**

The receptor binding assay is performed in a final volume of 200 μL binding buffer [10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01% BSA] and 1 nM [³H]-PGD₂ (Amersham Biosciences UK Ltd). Ligands are added in assay buffer containing a constant amount of DMSO (1% by volume).

Total binding is determined using 1% by volume of DMSO in assay buffer and non-specific binding is determined using 10 μM of unlabeled PGD₂ (Sigma). Human embryonic kidney (HEK) cell membranes (3.5 μg) expressing the CRTH2 receptor are incubated with 1.5 mg wheatgerm agglutinin SPA beads and 1 nM [³H]-PGD₂ (Amersham Biosciences UK Ltd) and the mixture incubated for 3 hours at room temperature. Bound [³H]-PGD₂ is detected using a Microbeta TRILUX liquid scintillation counter (Perkin Elmer). Compound IC₅₀ value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC₅₀ calculations are performed using Excel and XL fit (Microsoft), and this value is used to determine a Kᵢ value for the test compound using the Cheng-Prusoff equation.

**Biological Results**

The compounds of the Examples above were tested in the DP and CRTH2 radioligand binding assays. All compounds had Kᵢ values of less than 10 μM in both assay. For example, Example 1 had Kᵢ values of 320 and 390 nM in the DP and CRTH2 binding assays, respectively.
Claims

1. A compound of formula (I) for medicinal use:

\[
\begin{array}{c}
\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 \text{ and } \text{R}^5 \text{ independently represent hydrogen, halogen, } \\
-\text{S(O)}\text{R}^6, -\text{S(O)}_2\text{NR}^7\text{R}^8, -\text{NR}^7\text{S(O)}_2\text{R}^6, -\text{NR}^7\text{COR}^6, -\text{CONR}^7\text{R}^8, -\text{COR}^6, - \\
\text{NO}_2, -\text{CN}, -\text{OR}^7, \text{C}_r\text{C}_6\text{alkyl or C}_3\text{-C}_7\text{cycloalkyl, the latter two groups being } \\
\text{optionally substituted by one or more fluoro atoms; } \\
\text{R}^6 \text{ is C}_i\text{-C}_6\text{alkyl or C}_3\text{-C}_7\text{cycloalkyl, optionally substituted by one or more } \\
\text{fluoro atoms; } \\
\text{R}^7 \text{ and R}^8 \text{ independently represent hydrogen, C}_r\text{C}_6\text{alkyl or } \\
\text{C}_3\text{-C}_7\text{cycloalkyl, the latter two groups being optionally substituted by one or more } \\
\text{fluoro atoms; } \\
\text{A is } -\text{O}, -\text{S(O)}\text{R}^9, -\text{CR}^9\text{R}^{10}, -\text{NR}^{11} \text{ or } -\text{C(O)}; \\
\text{R}^9 \text{ and R}^{10} \text{ independently represent a hydrogen, fluoro or C}_i\text{-C}_6\text{alkyl; } \\
\text{R}^{11} \text{ and R}^{12} \text{ independently represent hydrogen or C}_i\text{-C}_6\text{alkyl; } \\
\text{B is } -\text{C(R}^9\text{R}^{10})\text{C(R}^9\text{R}^{10})^{-} \text{ or C(R}^{11})\text{=C(R}^{12})^{-}; \text{ and when A is } -\text{CR}^9\text{R}^{10}, \text{B may } \\
\text{additionally be } -\text{OCR}^9\text{R}^{10}, -\text{NR}^{11}\text{CR}^9\text{R}^{10} \text{ or } -\text{S(O)}\text{R}^9\text{CR}^9\text{R}^{10}; \\
\text{W is C}_r\text{C}_6\text{alkyl optionally substituted by one or more substituents } \\
\text{independently selected from fluoro, aryl, heteroaryl or C}_3\text{-C}_7\text{cycloalkyl, the latter } \\
\text{group being optionally substituted with one or more fluoro atoms; and } \\
\text{X is a carboxylic acid group, a tetrazolyl group, or a group of formula } \\
-\text{CONHS(O)}_2\text{R}^{13} \text{ or } -\text{S(O)}_2\text{NH}^{13}; \\
\text{R}^{13} \text{ is aryl, heteroaryl, C}_r\text{C}_6\text{alkyl or C}_3\text{-C}_7\text{cycloalkyl, the latter two groups } \\
\text{being optionally substituted by one or more fluoro atoms; and } \\
\text{n is O, 1 or 2.}
\end{array}
\]
2. A compound of formula (I) as defined in claim 1, excluding the compounds referred to and characterised in Examples 1-10 herein.

3. A pharmaceutical composition comprising a compound as defined in claim 1 or as claimed in claim 2, together with a pharmaceutically acceptable carrier.

4. The use of a compound as defined in claim 1 or as claimed in claim 2 in the manufacture of a medicament for use in the treatment of conditions responsive to modulation of DP and/or CRTH2 receptor activity.

5. A method of treatment of conditions responsive to modulation of DP and/or CRTH2 receptor activity, comprising administering to a patient suffering such disease an effective amount of a compound as defined in claim 1 or as claimed in claim 2.

6. The use as claimed in claim 4 or a method as claimed in claim 5, wherein the condition for treatment is selected from asthma, chronic obstructive pulmonary disease, allergic airway syndrome, bronchitis, cystic fibrosis, emphysema and rhinitis.

7. The use as claimed in claim 4 or a method as claimed in claim 5 wherein the condition for treatment is selected from psoriasis, atopic and non-atopic dermatitis Crohn’s disease, ulcerative colitis, and irritable bowel disease.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D215/36 A61K31/47 A61P25/00 A61P11/00 A61P17/00

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C

See patent family annex

**Date of the actual completion of the international search**

26 January 2010

**Date of mailing of the international search report**

12/02/2010

**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, Fax (+31-70) 340-3016

Bosrna, Peter

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### DOCUMENTS CONSIDERED TO BE RELEVANT

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