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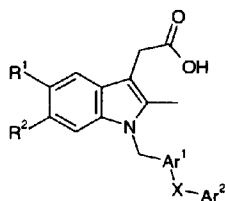
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(54) Title: INDOLES ACTIVE ON CRTH2 RECEPTOR



(I)

(57) Abstract: Indole derivatives having therapeutic utility are of formula (I): X is -SO<sub>2</sub>- or \*-SO<sub>2</sub>NR<sup>3</sup> - wherein the bond marked with an asterisk is attached to Ar<sup>1</sup>; R<sup>1</sup> and R<sup>2</sup> are, independently, hydrogen, fluoro, chloro, CN or CF<sub>3</sub>; R<sup>3</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub>alkyl or C<sub>3</sub>-C<sub>7</sub>cycloalkyl; and Ar<sup>1</sup> and Ar<sup>2</sup> are, independently, phenyl or a 5- or 6-membered heteroaryl group, wherein the phenyl or heteroaryl group is optionally substituted by one or more substituents independently selected from fluoro, chloro, CN, C<sub>3</sub>-C<sub>7</sub>cycloalkyl, -O(C<sub>1</sub>-C<sub>4</sub>alkyl) or C<sub>1</sub>-C<sub>6</sub>alkyl, the latter two groups being optionally substituted by one or more fluoro atoms.

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## INDOLES ACTIVE ON CRTH2 RECEPTOR

This invention relates to a class of indole 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**

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 D<sub>2</sub>, etc (Boyce; Allergy Asthma Proc., 2004, 25, 27-30). Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) is the major metabolite produced by the action of cyclooxygenase on arachadonic acid by mast cells in response to allergen challenge (Lewis *et al*; J. Immunol., 1982, 129, 1627-1631). It has been shown that PGD<sub>2</sub> 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. Head Neck Surg., 1987, 113, 179-183; Lebel *et al*; J. Allergy Clin. Immunol., 1988, 82, 869-877), bronchial asthma (Murray *et al*; N. Engl. J. Med., 1986, 315, 800-804; Liu *et al*; Am. Rev. Respir. Dis., 1990, 142, 126-132; Wenzel *et al*; J. Allergy Clin. Immunol., 1991, 87, 540-548), and urticaria (Heavey *et al*; J. Allergy Clin. Immunol., 1986, 78, 458-461). PGD<sub>2</sub> mediates its effects through two receptors, the PGD<sub>2</sub> (or DP) receptor (Boie *et al*; J. Biol. Chem., 1995, 270, 18910-18916) and the chemoattractant receptor-homologous molecule expressed on Th2 (or CRTH2) (Nagata *et al*; J. Immunol., 1999, 162, 1278-1289; Powell; Prostaglandins Luekot. Essent. Fatty Acids, 2003, 69, 179-185). Therefore, it has been postulated that agents that antagonise the effects of PGD<sub>2</sub> at its receptors may have beneficial effects in number of disease states.

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 PGD<sub>2</sub>-mediated cell migration in these cell types (Hirai *et al*; J. Exp. Med., 2001, 193, 255-261), and also to play

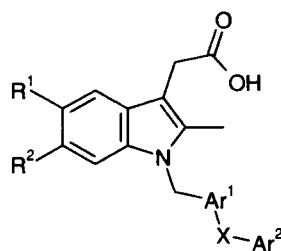
a major role in neutrophil and eosinophil cell recruitment in a model of contact dermatitis (Takeshita et al; *Int. Immunol.*, 2004, 16, 947-959). Ramatroban {(3R)-3-[(4-fluorophenyl)sulphonylamino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid}, a dual CRTH2 and thromboxane A<sub>2</sub> receptor antagonist, has been shown to attenuate these responses (Sugimoto et al; *J. Pharmacol. Exp. Ther.*, 2003, 305, 347-352; Takeshita et al; *op. cit.*). The potential of PGD<sub>2</sub> both to enhance allergic inflammation and induce an inflammatory response has been demonstrated in mice and rats. Transgenic mice over expressing PGD<sub>2</sub> synthase exhibit an enhanced pulmonary eosinophilia and increased levels of Th2 cytokines in response to allergen challenge (Fujitani et al, *J. Immunol.*, 2002, 168, 443-449). 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 but a DP agonist (BW 245C) or a TP agonist (I-BOP) showed no effect (Shirashi et al; *J. Pharmacol. Exp Ther.*, 2005, 312, 954-960). These observations suggest that CRTH2 antagonists may have valuable properties for the treatment of diseases mediated by PGD<sub>2</sub>.

In addition to Ramatroban a number of other CRTH2 antagonists have been described. Examples include: indoleacetic acids (WO2007/065684; WO2007/045867; WO2006/034419; WO2005/094816; WO2005/044260; WO2005/040114; WO2005/040112; GB2407318; WO2005/019171; WO2004/106302; WO2004/078719; WO2004/007451; WO2003/101981; WO2003/101961; WO2003/097598; WO2003/097042; WO2003/066047; WO2003/066046; WO2003/022813), quinolines (WO2007/036743), tetrahydroquinolines (WO2006/091674; US2005/256158; WO2005/100321; WO2005/007094; WO2004/035543; WO2004/032848; EP1435356; EP1413306), phenoxyacetic acids (WO2007/062678; WO2007/062773; WO2006/125596; WO2006/125593; WO2006/056752; WO2005/115382; WO2005/105727; WO2005/018529; WO2004/089885; WO2004/089884) and phenylacetic acids (WO2004/058164).

### **Detailed Description of the Invention**

One aspect of the invention provides indole derivatives of formula (I):

3



(I)

X is  $-\text{SO}_2-$  or  $^*-\text{SO}_2\text{NR}^3-$  wherein the bond marked with an asterisk is  
 5 attached to  $\text{Ar}^1$ ;

$\text{R}^1$  and  $\text{R}^2$  are, independently, hydrogen, fluoro, chloro, CN or  $\text{CF}_3$ ;

$\text{R}^3$  is hydrogen,  $\text{C}_1$ - $\text{C}_8$ alkyl or  $\text{C}_3$ - $\text{C}_7$ cycloalkyl;

$\text{Ar}^1$  and  $\text{Ar}^2$  are, independently, phenyl or 5- or 6-membered heteroaryl  
 group, wherein the phenyl or heteroaryl groups are optionally substituted by one  
 10 or more substituents independently selected from fluoro, chloro, CN,  
 $\text{C}_3$ - $\text{C}_7$ cycloalkyl,  $-\text{O}(\text{C}_1$ - $\text{C}_4$ alkyl) or  $\text{C}_1$ - $\text{C}_6$ alkyl, the latter two groups being  
 optionally substituted by one or more fluoro atoms.

Compounds (I) with which the invention is concerned are CRTH2  
 receptor antagonists, but they may also have beneficial effects at other  
 15 prostanoid receptors, such as the  $\text{PGD}_2$  receptor or the thromboxane  $\text{A}_2$   
 receptor.

Compounds of formula (I) above may be prepared or recovered in the  
 form of salts, and in some cases as *N*-oxides, hydrates, and solvates thereof.  
 Any reference herein, including the claims herein, to "compounds of the  
 20 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.

The invention also includes (i) use of a compound with which the  
 25 invention is concerned in the manufacture of a medicament for use in the  
 treatment of conditions responsive to modulation of CRTH2 receptor activity,  
 and (ii) a method of treatment of conditions responsive to modulation of 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 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 Nodosa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fasciitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

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<sub>a</sub>-C<sub>b</sub>)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,  
5 ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

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

10 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  
15 naphthyl.

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  
20 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.

25 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  
30 organic bases, for example *N*-methyl-D-glucamine, choline tris(hydroxymethyl)aminomethane, 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, benzenesulfonic, 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), naphthalenylsulfonates (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.

Salts are discussed in the "Handbook of Pharmaceutical Salts. Properties, selection and use", P. Heinrich Stahl & Camille G. Wermuth, Wiley-VCH, 2002.

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- $\beta$ -hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, 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.

10 **Structural aspects of compounds with which the invention is concerned**

$R^1$  and  $R^2$  are, independently, hydrogen, fluoro, chloro, CN or  $CF_3$ . In one subset of compounds of the invention  $R^1$  is fluoro and  $R^2$  is hydrogen. In another subset of compounds of the invention  $R^1$  is hydrogen and  $R^2$  is fluoro. All combinations of the permitted substituents  $R^1$  and  $R^2$  are allowed.

15  $Ar^1$  and  $Ar^2$  are, independently, phenyl or 5- or 6-membered heteroaryl. Examples of such rings include phenyl, pyrrole, imidazole, furan, thiophene, oxazole, thiazole, pyrazole, isoxazole, isothiazole, pyridine, pyridazine, pyrimidine and pyrazine. Currently preferred is the case where both  $Ar^1$  and  $Ar^2$  are phenyl rings.

20  $Ar^1$  and  $Ar^2$  may be optionally be substituted by one or more substituents independently selected from fluoro, chloro, CN,  $C_3$ - $C_7$ cycloalkyl such as cyclopropyl,  $-O(C_1$ - $C_4$ alkyl) such as methoxy,  $C_1$ - $C_6$ alkyl such as methyl or the latter two groups being optionally substituted by one or more fluoro atoms, as in the case of trifluoromethoxy or trifluoromethyl.

25 Currently it is preferred that the radical  $Ar^2X$ - is in the para-, or more preferably the ortho-position of the ring  $Ar^1$  relative to the point of attachment of  $Ar^1$  to the rest of the molecule.

Specific compounds of the invention include those of the Examples herein.

30 **Compositions**

As mentioned above, the compounds with which the invention is concerned are 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, bronchitis and chronic obstructive pulmonary disease.

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  
5 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  
10 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,  
15 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  
20 vehicle.

Other compounds may be combined with compounds with which the invention is concerned for the prevention and treatment of prostaglandin-mediated diseases. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating PGD<sub>2</sub>-mediated  
25 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)  $\beta$ 2-adrenoreceptor agonists, such as salmeterol, indacaterol or formoterol; (3)  
30 leukotriene modulators, for example leukotriene antagonists such as montelukast, zafirluast 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, citirizine, loratidine or astemizole; (7) antitussive agents, such as codeine or dexamorphan; (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  
5 antagonists, such as those described in WO97/03094 and WO97/02289; (11) TACE inhibitors and TNF- $\alpha$  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  
10 WO2005/026124, WO2003/053930 and WO06/082412; (14) A2a agonists such as those described in EP1052264 and EP1241176 (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  
15 A<sub>2</sub> 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.

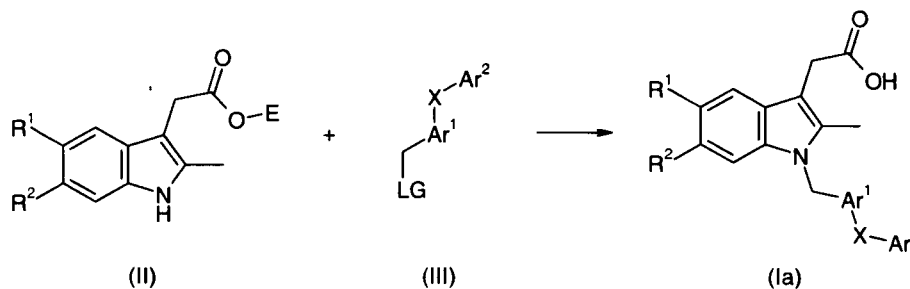
## 20 **Synthesis**

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  
25 literature and are well-known to the one skilled in the art. Typical literature sources are "*Advanced organic chemistry*", 4<sup>th</sup> Edition (Wiley), J. March, "*Comprehensive Organic Transformation*", 2<sup>nd</sup> Edition (Wiley), R. C. Larock, "*Handbook of Heterocyclic Chemistry*", 2<sup>nd</sup> Edition (Pergamon), A. R. Katritzky, review articles such as found in "*Synthesis*", "*Acc. Chem. Res.*", "*Chem. Rev.*",  
30 or primary literature sources identified by standard literature searches online or from secondary sources such as "*Chemical Abstracts*" or "*Beilstein*". The extensive literature relating to the synthesis of indole compounds is especially relevant, of course.

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.

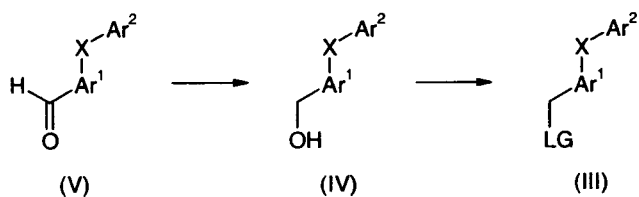
The compounds of the invention of formula (I) may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free acid form corresponding to isolated salts can be generated by acidification with a suitable acid such as acetic acid and hydrochloric 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 formula (Ia), wherein X, R<sup>1</sup>, R<sup>2</sup>, Ar<sup>1</sup> and Ar<sup>2</sup> are as defined for formula (I) above, may be prepared by the reaction between an indole of formula (II), wherein E represents hydrogen or alkyl group, and a suitable alkylating agent of formula (III), wherein LG represents a suitable leaving group (for example, chloro, bromo or methanesulfonyloxy) (Scheme 1). Typically, the alkylation reaction is carried out in the presence of base (for example, sodium hydride or potassium carbonate) in an inert solvent (for example, dimethyl sulfoxide or *N,N*-dimethylformamide). It is to be understood that if the reaction is carried out on a protected form of (II) an appropriate deprotection step will be required to obtain the desired compound of the invention (Ia).



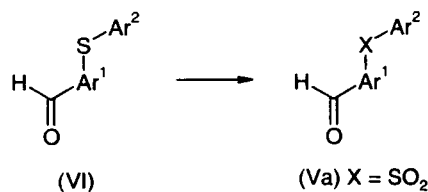
Scheme 1

Compounds of formula (II) are commercially available or can be prepared by known methods. Compounds of formula (III) may be prepared by the reduction of compounds of formula (V) to an intermediate alcohol of formula (IV), followed by reaction with an appropriate halogenating (for example, phosphorus tribromide) or triflating (for example, triflic anhydride) agent (Scheme 2).



Scheme 2

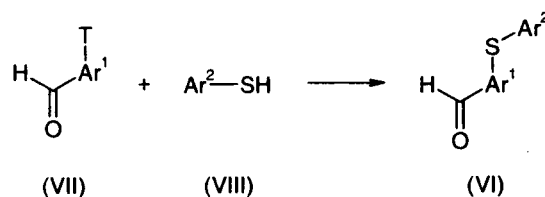
Compounds of formula (Va), wherein X represents SO<sub>2</sub> group, may be prepared by the oxidation of compounds of formula (VI), with a suitable oxidising agent such as potassium peroxymonosulfate, *meta*-chloroperoxybenzoic acid or other well known oxidising agents (Scheme 3).



Scheme 3

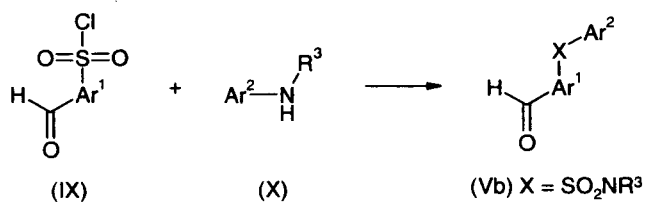
Compounds of formula (VI) may be prepared from intermediate compounds of formula (VII), wherein T represents a chloro, bromo, or iodo atom, or a trifluoromethanesulfonyloxy group, by reaction with a thiol of formula (VIII) in the presence of a suitable base such as potassium carbonate (Scheme 4). Alternatively, the reaction may be carried out in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium(0) in a protic solvent such as ethanol. Compounds of formula (VII) and (VIII) are commercially available or can be prepared by known methods.

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Scheme 4

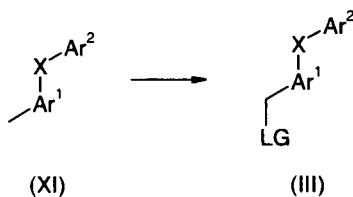
Compounds of formula (Vb), wherein X represents  $\text{SO}_2\text{NR}^3$  group, may be prepared by the reaction between a compound of formula (IX) and an amine of formula (X) (Scheme 5). The reaction may be carried out in the presence of a suitable base (for example, triethylamine or diisopropylethylamine) and solvent (for example, dichloromethane or dichloroethane), at temperatures ranging from  $0^\circ\text{C}$  to the reflux temperature of the solvent, preferably at about room temperature. Compounds of formula (IX) and (X) are commercially available or can be prepared by known methods.



Scheme 5

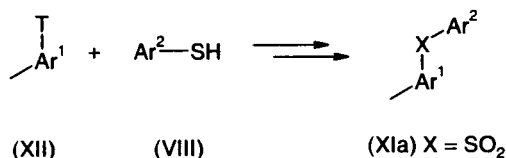
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Alternatively, intermediate compounds of formula (III), wherein LG represents a chloro or bromo group, may be prepared from compounds of formula (XI) by treatment with *N*-chlorosuccinimide or *N*-bromosuccinimide in the presence of a suitable radical initiator (for example, 2,2'-azobisisobutyronitrile or benzoyl peroxide) (Scheme 6).



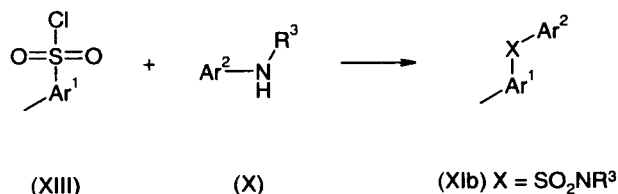
Scheme 6

Compounds of formula (XIa), wherein X represents SO<sub>2</sub> group, may be prepared from compounds of formula (VIII) and (XII) (Scheme 7), using methods described above for the preparation of compounds of formula (Va) from compounds of formula (VII) and (VIII) (Schemes 3 and 4). Compounds of formula (XII) are commercially available or can be prepared by known methods.



Scheme 7

Compounds of formula (XIb), wherein X represents SO<sub>2</sub>NR<sup>3</sup> group, may be prepared from compounds of formula (X) and (XIII) (Scheme 8), using methods described above for the preparation of compounds of formula (Vb) from compounds of formula (X) and (XI) (Scheme 5). Compounds of formula (XIII) are commercially available or can be prepared by known methods.



Scheme 8

### Examples

<sup>1</sup>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 s = broad singlet, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

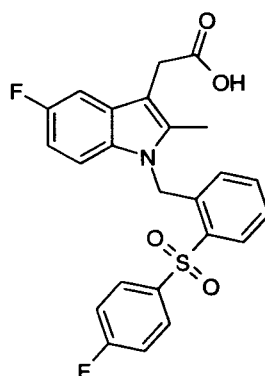
Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: experiments 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  $\mu$ m 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.

Method B: experiments were performed on a Micromass Platform LC spectrometer with positive and negative ion electrospray and ELS / Diode array detection using a Phenomenex Luna C18(2) 30 x 4.6 mm column and a 2 mL / minute flow rate. The solvent system was 95% solvent A and 5% solvent B for the first 0.50 minutes followed by a gradient up to 5% solvent A and 95% solvent B over the next 4 minutes. The final solvent system was held constant for a further 0.50 minutes

**Example 1: {5-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid**



**Preparation 1a: 2-(4-fluorobenzenesulfonyl)benzaldehyde**

A solution of 2-(4-fluorophenylsulfonyl)benzaldehyde (1.0 g) in dichloromethane (43 mL) was treated portionwise with 3-chloroperoxybenzoic acid (2.9 g), and the resulting mixture was stirred at room temperature for 2 hours. The mixture was diluted with saturated aqueous sodium thiosulphate solution and extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate solution (3 x 25 mL) and saturated aqueous sodium chloride solution (20 mL), and then dried

over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a white solid (0.89 g).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.22 (m, 2H), 7.72-7.80 (m, 2H), 7.93 (m, 2H), 8.03 (m, 1H), 8.17 (m, 1H), 10.84 (s, 1H).

5 **Preparation 1b: [2-(4-fluorobenzenesulfonyl)phenyl]methanol**

A solution of 2-(4-fluorobenzenesulfonyl)benzaldehyde (0.89 g) in methanol (34 mL) at  $0^\circ\text{C}$  was treated with sodium borohydride (0.038 g), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was diluted with 1.0 M aqueous hydrochloric acid (3.0 mL) and concentrated under  
10 reduced pressure. The residue was diluted with diethyl ether, washed with water (2 x 20 mL) and saturated aqueous sodium chloride solution (10 mL), and then dried over magnesium sulfate. The solvent was removed under reduced pressure to afford title compound as a colourless oil (0.89 g).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.99 (br s, 1H), 4.76 (d,  $J = 5.0$ , 2H), 7.20 (m, 2H),  
15 7.52 (ddd,  $J = 1.5$ , 7.8, 7.8 Hz, 2H), 7.58 (dd,  $J = 1.3$ , 7.5 Hz, 1H), 7.64 (ddd,  $J = 1.4$ , 7.5, 7.5 Hz, 1H), 7.92 (m, 2H), 8.10 (dd,  $J = 1.3$ , 7.9 Hz, 1H).

**Preparation 1c: Preparation of 2-(4-fluorobenzenesulfonyl)benzyl bromide**

A solution of [2-(4-fluorobenzenesulfonyl)phenyl]methanol (0.86 g) in dichloromethane (16 mL) at  $0^\circ\text{C}$  was treated with phosphorus tribromide  
20 (0.30 mL), and the resulting mixture was stirred at room temperature for 10 minutes. The mixture was poured into a mixture of saturated aqueous sodium thiosulphate solution (30 mL) and saturated aqueous sodium chloride solution (20 mL). The aqueous phase was extracted with dichloromethane (2 x 20 mL), and the combined organic phases were dried over magnesium sulfate and  
25 concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 3:2 by volume) to afford the title compound as a colourless oil (0.27 g).

$^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  4.89 (s, 2H), 7.20 (m, 2H), 7.51 (ddd,  $J = 1.7$ , 7.1, 8.3  
30 Hz, 1H), 7.57 (dd,  $J = 1.7$ , 7.8 Hz, 1H), 7.61 (ddd,  $J = 1.7$ , 7.0, 7.8 Hz, 1H), 7.94 (m, 2H), 8.17 (dd,  $J = 1.4$ , 8.0 Hz, 1H).

**Preparation 1d: {5-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indolyl}acetic acid ethyl ester**

A solution of (5-fluoro-2-methyl-1H-indol-3-yl)acetic acid ethyl ester (0.064 g) in dimethyl sulfoxide (1.4 mL) was treated with sodium hydride (60% slurry in mineral oil, 0.016 g), and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was treated with 2-(4-fluorobenzenesulfonyl)benzyl bromide (0.13 g) and potassium iodide (0.068 g), and the resulting mixture was stirred at room temperature for 12 hours, and then diluted with saturated aqueous ammonium chloride solution (2.0 mL) and water (25 mL). The mixture was extracted with ethyl acetate (3 x 10 mL), and the combined extracts were washed with saturated aqueous sodium chloride solution (2.0 mL) and dried over magnesium sulphate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 3:2 by volume) to afford the title compound as a colourless oil (0.079 g).

MS: ESI (+ve) (Method B): 484 (M+H)<sup>+</sup>, Retention time 4.3 min.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.24 (t, J = 7.1 Hz, 3H), 2.05 (s, 3H), 3.65 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 5.48 (s, 2H), 6.27 (d, J = 7.8 Hz, 1H), 6.52 (dd, J = 4.1, 8.8 Hz, 1H), 6.73 (ddd, J = 2.4, 9.0, 9.0 Hz, 1H), 7.21 (dd, J = 2.3, 9.4 Hz, 1H), 7.28 (m, 2H), 7.37 (ddd, J = 1.4, 7.7, 7.7 Hz, 1H), 7.45 (dd, J = 7.7, 7.7, 1.2 Hz, 1H), 8.00 (m, 2H), 8.21 (dd, J = 7.8, 1.4 Hz, 1H).

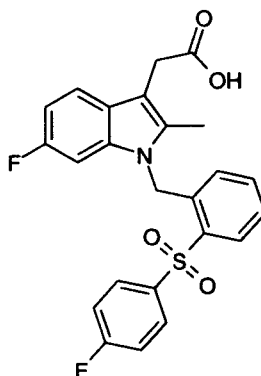
**Preparation 1e: {5-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid**

A solution of {5-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indolyl}acetic acid ethyl ester (0.041 g) in tetrahydrofuran (1.4 mL) was treated with 2.0 M aqueous lithium hydroxide solution (1.4 mL), and the resulting mixture was stirred at room temperature for 17 hours. The mixture was diluted with water (10 mL), pH adjusted to 4 by the addition of 1.0 M aqueous hydrochloric acid and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with saturated aqueous sodium chloride solution (2.0 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by preparative reverse-phase HPLC to afford the title compound as a white solid (0.023 g).

MS: ESI (+ve) (Method A): 456 (M+H)<sup>+</sup>, Retention time 11.2 min.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.91 (s, 1H), 3.56 (s, 2H), 5.48 (s, 2H), 6.13 (d, J = 7.5 Hz, 1H), 6.66-6.75 (m, 2H), 7.19 (dd, J = 2.2, 10.0 Hz, 1H), 7.46-7.57 (m, 4H), 8.11 (m, 2H), 8.17 (dd, J = 1.4, 7.7 Hz, 1H), 12.14 (br s, 1H).

**Example 2: {6-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid**



**Preparation 2a: (6-fluoro-2-methyl-1H-indol-3-yl)acetic acid ethyl ester**

A mixture of (3-fluorophenyl)hydrazine hydrochloride salt (3.5 g), 4-oxo-  
10 pentanoic acid (2.3 g) and ethanol (24 mL) was treated with sulfuric acid (2.0 mL), and the resulting reaction mixture was stirred at 85°C for 3 days. The mixture was cooled to room temperature, poured onto a mixture of ice and water and extracted with dichloromethane (3 x 50 mL). The combined extracts were washed with saturated aqueous sodium chloride solution (2.0 mL) and dried  
15 over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel, eluting with a mixture of cyclohexane, ethyl acetate and formic acid (1:0:0.001 to 0:1:0.001 by volume) to afford the title compound as a yellow oil (0.40 g).

MS: ESI (+ve) (Method B): 236 (M+H)<sup>+</sup>, Retention time 3.5 min.

**20 Preparation 2b: {6-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid ethyl ester**

The title compound was prepared by the method of Preparation 1d using (6-fluoro-2-methyl-1H-indol-3-yl)acetic acid ethyl ester and 2-(4-fluorobenzenesulfonyl)benzyl bromide.

25 MS: ESI (+ve) (Method B): 484 (M+H)<sup>+</sup>, Retention time 4.2 min.

$^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  1.23 (t, J = 7.1 Hz, 3H), 2.07 (s, 3H), 3.67 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 5.43 (s, 2H), 6.17 (dd, J = 2.1, 9.7 Hz, 1H), 6.33 (dd, J =

1.0, 7.7 Hz, 1H), 6.83 (dt,  $J = 2.2, 8.5$  Hz, 1H), 7.38 (m, 5H), 8.00 (m, 2H), 8.24 (dd,  $J = 1.3, 7.7$  Hz, 1H) 12.6 (br s, 1H).

**Preparation 2c: {6-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indol-3-yl}acetic acid**

5 A solution of {6-fluoro-1-[2-(4-fluorobenzenesulfonyl)benzyl]-2-methyl-1H-indolyl}acetic acid ethyl ester (0.095 g) in tetrahydrofuran (5.0 mL) was treated with 1.0 M aqueous lithium hydroxide solution (0.5 mL), and the resulting mixture was stirred at room temperature for 22 hours. The mixture was diluted with water (10 mL), pH adjusted to 5 by the addition of 1.0 M aqueous hydrochloric acid and extracted with ethyl acetate (3 x 10 mL). The combined extracts were washed with saturated aqueous sodium chloride solution (2.0 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel, eluting with a mixture of dichloromethane, ethyl acetate and formic acid (1:0:0.001 to 0:1:0.001  
10 by volume) to afford the title compound as a white solid (0.067 g).  
15

MS: ESI (+ve) (Method A): 456 (M+H)<sup>+</sup>, Retention time 11.2 min.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.94 (s, 3H), 3.61 (s, 2H), 5.49 (s, 2H), 6.22 (d,  $J = 7.4$  Hz, 1H), 6.46 (dd,  $J = 2.2, 10.2$  Hz, 1H), 6.83 (m, 1H), 7.44 (dd,  $J = 5.5, 8.7$  Hz, 1H), 7.54 (m, 4H), 8.16 (m, 2H), 8.24 (dd,  $J = 1.4, 7.7$  Hz, 1H).

20 **Biological Methods**

Compounds of the invention were tested using the following biological test method to determine their ability to displace PGD<sub>2</sub> from the CRTH2 receptor.

**CRTH2 Radioligand Binding Assay**

25 The receptor binding assay is performed in a final volume of 200  $\mu$ L binding buffer [10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01% BSA] and 1 nM [<sup>3</sup>H]-PGD<sub>2</sub> (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  $\mu$ M of unlabeled PGD<sub>2</sub> (Sigma).  
30 Human embryonic kidney (HEK) cell membranes (3.5  $\mu$ g) expressing the CRTH2 receptor are incubated with 1.5 mg wheatgerm agglutinin SPA beads and 1 nM [<sup>3</sup>H]-PGD<sub>2</sub> (Amersham Biosciences UK Ltd) and the mixture incubated for 3 hours at room temperature. Bound [<sup>3</sup>H]-PGD<sub>2</sub> is detected using a Microbeta

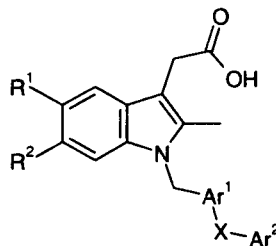
TRILUX liquid scintillation counter (Perkin Elmer). Compound  $IC_{50}$  value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series.  $IC_{50}$  calculations are performed using Excel and XLfit (Microsoft), and this value is used to determine a  $K_i$  value for the test compound using the Cheng-Prusoff equation.

#### Biological Results

All compounds of the Examples above were tested in the CRTH2 radioligand binding assay described above; the compounds had a  $K_i$  value of less than 1  $\mu$ M in the binding assay. For example, Example 1 had a  $K_i$  value of 66 nM.

**Claims:**

1. A compound which is an indole derivative of formula (I):



(I)

5

X is  $-\text{SO}_2-$  or  $^*-\text{SO}_2\text{NR}^3-$  wherein the bond marked with an asterisk is attached to  $\text{Ar}^1$ ;

$\text{R}^1$  and  $\text{R}^2$  are, independently, hydrogen, fluoro, chloro, CN or  $\text{CF}_3$ ;

$\text{R}^3$  is hydrogen,  $\text{C}_1$ - $\text{C}_8$ alkyl or  $\text{C}_3$ - $\text{C}_7$ cycloalkyl; and

- 10  $\text{Ar}^1$  and  $\text{Ar}^2$  are, independently, phenyl or a 5- or 6-membered heteroaryl group, wherein the phenyl or heteroaryl group is optionally substituted by one or more substituents independently selected from fluoro, chloro, CN,  $\text{C}_3$ - $\text{C}_7$ cycloalkyl,  $-\text{O}(\text{C}_1$ - $\text{C}_4$ alkyl) or  $\text{C}_1$ - $\text{C}_6$ alkyl, the latter two groups being optionally substituted by one or more fluoro atoms.

- 15 2. A compound as claimed in claim 1 wherein  $\text{R}^2$  is hydrogen and  $\text{R}^1$  is fluoro.

3. A compound as claimed in claim 1 wherein  $\text{R}^2$  is fluoro and  $\text{R}^1$  is hydrogen.

- 20 4. A compound as claimed in any of the preceding claims wherein ring  $\text{Ar}^1$  is a phenyl ring.

5. A compound as claimed in any of the preceding claims wherein ring  $\text{Ar}^2$  is a phenyl ring.

6. A compound as claimed in any of the preceding claims wherein optional substituents in  $\text{Ar}^1$  and  $\text{Ar}^2$  are selected from chloro, fluoro,  $-\text{CN}$ , methyl, ethyl, 25 isopropyl, cyclopropyl, trifluoromethyl, methoxy, isopropoxy, cyclopropoxy, and trifluoromethoxy.

7. A compound as claimed in any of the preceding claims wherein the radical  $\text{Ar}^2\text{X}-$  is in the ortho-position of the ring  $\text{Ar}^1$  relative to the point of attachment of  $\text{Ar}^1$  to the rest of the molecule.

8. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier.
9. Use of a compound as claimed in any of claims 1 to 7 for the manufacture of a composition for the treatment of asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome, or allergic rhinobronchitis.
- 5 10. Use of a compound as claimed in any of claims 1 to 7 for the manufacture of a composition for the treatment of psoriasis, atopic and non-atopic dermatitis, Crohn's disease, ulcerative colitis, or irritable bowel disease.
- 10 11. A method of treatment of asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome, or allergic rhinobronchitis, comprising administering to a patient suffering such disease an effective amount of a compound as claimed in any of claims 1 to 7.
- 15 12. A method of treatment of psoriasis, atopic and non-atopic dermatitis, Crohn's disease, ulcerative colitis, or irritable bowel disease, comprising administering to a patient suffering such disease an effective amount of a compound as claimed in any of claims 1 to 7.

**INTERNATIONAL SEARCH REPORT**

International application No  
PCT/GB2009/000124

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. C07D209/22 A61K31/405 A61P29/00

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

**B. FIELDS SEARCHED**

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

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

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

EPO-Internal, WPI Data, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/065684 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; SANDHAM DAVID ANDREW [GB]) 14 June 2007 (2007-06-14) cited in the application claim 1; examples 3-6	1-12
Y	GB 2 407 318 A (OXAGEN LTD [GB]) 27 April 2005 (2005-04-27) cited in the application claims 1-22; example 12	1-12
Y	WO 2004/058164 A (TULARIK INC [US]) 15 July 2004 (2004-07-15) cited in the application example 61	1-12
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Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
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- \*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
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Date of the actual completion of the international search

20 March 2009

Date of mailing of the international search report

02/04/2009

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Authorized officer

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2009/000124

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PETTIPHER ROY ET AL: "Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases."            NATURE REVIEWS. DRUG DISCOVERY APR 2007, vol. 6, no. 4, April 2007 (2007-04), pages 313-325, XP002520111            ISSN: 1474-1776            the whole document</p>	1-12
A	<p>WO 03/066047 A (ASTRAZENECA AB [SE]; BAXTER ANDREW [GB]; STEELE JOHN [GB]; TEAGUE SIMO) 14 August 2003 (2003-08-14) cited in the application</p>	
A	<p>NORMAN P: "Indole-based CRTH2 antagonists"            EXPERT OPINION ON THERAPEUTIC PATENTS, INFORMA HEALTHCARE, GB, vol. 15, no. 12, 1 December 2005 (2005-12-01), pages 1817-1823, XP002475828            ISSN: 1354-3776</p>	
A	<p>LY TAI WEI ET AL: "Small-molecule CRTH2 antagonists for the treatment of allergic inflammation: an overview."            EXPERT OPINION ON INVESTIGATIONAL DRUGS JUL 2005, vol. 14, no. 7, July 2005 (2005-07), pages 769-773, XP002520112            ISSN: 1744-7658</p>	
A	<p>ULVEN TROND ET AL: "Targeting the prostaglandin D2 receptors DP and CRTH2 for treatment of inflammation."            CURRENT TOPICS IN MEDICINAL CHEMISTRY 2006, vol. 6, no. 13, 2006, pages 1427-1444, XP008104082            ISSN: 1568-0266</p>	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2009/000124

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