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### COMPOUNDS HAVING CRTH2 ANTAGONIST ACTIVITY

The present invention relates to compounds which are useful as pharmaceuticals, to methods for preparing these compounds, compositions containing them and their use  
5 in the treatment and prevention of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis and other inflammatory diseases mediated by prostaglandin D<sub>2</sub> (PGD<sub>2</sub>) or other agonists acting at the CRTH2 receptor on cells including eosinophils, basophils and Th2 lymphocytes.

10 PGD<sub>2</sub> is an eicosanoid, a class of chemical mediator synthesised by cells in response to local tissue damage, normal stimuli or hormonal stimuli or *via* cellular activation pathways. Eicosanoids bind to specific cell surface receptors on a wide variety of tissues throughout the body and mediate various effects in these tissues. PGD<sub>2</sub> is known to be produced by mast cells, macrophages and Th2 lymphocytes and has  
15 been detected in high concentrations in the airways of asthmatic patients challenged with antigen (Murray *et al.*, (1986), *N. Engl. J. Med.* **315**: 800-804). Instillation of PGD<sub>2</sub> into airways can provoke many features of the asthmatic response including bronchoconstriction (Hardy *et al.*, (1984) *N. Engl. J. Med.* **311**: 209-213; Sampson *et al.*, (1997) *Thorax* **52**: 513-518) and eosinophil accumulation (Emery *et al.*, (1989) *J. Appl. Physiol.* **67**: 959-962).  
20

The potential of exogenously applied PGD<sub>2</sub> to induce inflammatory responses has been confirmed by the use of transgenic mice overexpressing human PGD<sub>2</sub> synthase which exhibit exaggerated eosinophilic lung inflammation and Th2 cytokine  
25 production in response to antigen (Fujitani *et al.*, (2002) *J. Immunol.* **168**: 443-449).

The first receptor specific for PGD<sub>2</sub> to be discovered was the DP receptor which is linked to elevation of the intracellular levels of cAMP. However, PGD<sub>2</sub> is thought to mediate much of its proinflammatory activity through interaction with a G protein-coupled receptor termed CRTH2 (chemoattractant receptor-homologous molecule  
30 expressed on Th2 cells) which is expressed by Th2 lymphocytes, eosinophils and



\*ACTION\*

basophils (Hirai *et al*, (2001) *J. Exp. Med.* **193**: 255-261, and EP0851030 and EP-A-1211513 and Bauer *et al*, EP-A-1170594). It seems clear that the effect of PGD<sub>2</sub> on the activation of Th2 lymphocytes and eosinophils is mediated through CRTH2 since the selective CRTH2 agonists 13,14 dihydro-15-keto-PGD<sub>2</sub> (DK-PGD<sub>2</sub>) and 15R-methyl-PGD<sub>2</sub> can elicit this response and the effects of PGD<sub>2</sub> are blocked by an anti-  
5 CRTH2 antibody (Hirai *et al*, 2001; Monneret *et al*, (2003) *J. Pharmacol. Exp. Ther.* **304**: 349-355). In contrast, the selective DP agonist BW245C does not promote migration of Th2 lymphocytes or eosinophils (Hirai *et al*, 2001; Gervais *et al*, (2001) *J. Allergy Clin. Immunol.* **108**: 982-988). Based on this evidence, antagonising PGD<sub>2</sub>  
10 at the CRTH2 receptor is an attractive approach to treat the inflammatory component of Th2-dependent allergic diseases such as asthma, allergic rhinitis and atopic dermatitis.

EP-A-1170594 suggests that the method to which it relates can be used to identify  
15 compounds which are of use in the treatment of allergic asthma, atopic dermatitis, allergic rhinitis, autoimmune, reperfusion injury and a number of inflammatory conditions, all of which are mediated by the action of PGD<sub>2</sub> or other agonists at the CRTH2 receptor.

20 Compounds which bind to CRTH2 are taught in WO-A-03066046 and WO-A-03066047. These compounds are not new but were first disclosed, along with similar compounds, in GB 1356834, GB 1407658 and GB 1460348, where they were said to have anti-inflammatory, analgesic and antipyretic activity. WO-A-03066046 and WO-A-03066047 teach that the compounds to which they relate are modulators of  
25 CRTH2 receptor activity and are therefore of use in the treatment or prevention of obstructive airway diseases such as asthma, chronic obstructive pulmonary disease (COPD) and a number of other diseases including various conditions of bones and joints, skin and eyes, GI tract, central and peripheral nervous system and other tissues as well as allograft rejection. These compounds are all indole derivatives  
30 with an acetic acid substituent at the 3-position of the indole ring.

PL 65781 and JP 43-24418 also relate to indole-3 acetic acid derivatives which are similar in structure to indomethacin and, like indomethacin, are said to have anti-inflammatory and antipyretic activity. Thus, although this may not have been appreciated at the time when these documents were published, the compounds they describe are COX inhibitors, an activity which is quite different from that of the compounds of the present invention. Indeed, COX inhibitors are contraindicated in the treatment of many of the diseases and conditions, for example asthma and inflammatory bowel disease for which the compounds of the present invention are useful, although they may sometimes be used to treat arthritic conditions.

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There is further prior art which relates to indole-1-acetic acid compounds, although these are not described as CRTH2 antagonists. For example WO-A-9950268, WO-A-0032180, WO-A-0151849 and WO-A-0164205 all relate to compounds which are indole-1-acetic acid derivatives but these compounds are said to be aldose reductase inhibitors useful in the treatment of diabetes mellitus (WO-A-9950268, WO-A-0032180 and WO-A-0164205) or hypouricemic agents (WO-A-0151849). There is no suggestion in any of these documents that the compounds would be useful for the treatment of diseases and conditions mediated by PGD<sub>2</sub> or other CRTH2 receptor agonists.

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US 4,363,912 relates to indole-1-acetic acid derivatives which are said to be inhibitors of thromboxane synthetase and to be useful in the treatment of conditions such as thrombosis, ischaemic heart disease and stroke.

WO-A-9603376 relates to compounds which are said to be sPLA<sub>2</sub> inhibitors which are useful in the treatment of bronchial asthma and allergic rhinitis. These compounds all have amide or hydrazide substituents in place of the carboxylic acid derivative of the compounds of the present invention.

JP 2001247570 relates to a method of producing a 3-benzothiazolylmethyl indole acetic acid, which is said to be an aldose reductase inhibitor.

US 4,859,692 relates to compounds which are said to be leukotriene antagonists useful in the treatment of conditions such as asthma, hay fever and allergic rhinitis as well as certain inflammatory conditions such as bronchitis, atopic and ectopic  
5 eczema. Some of the compounds of this document are indole-1-acetic acids but the same authors, in *J. Med. Chem.*, 6(33), 1781-1790 (1990), teach that compounds with an acetic acid group on the indole nitrogen do not have significant peptidoleukotriene activity. In view of this, it is most surprising that the compounds of the present invention, which all have an acetic acid group on the indole nitrogen, are useful for  
10 treating conditions such as asthma, hay fever and allergic rhinitis.

US 4,273,782 is directed to indole-1-acetic acid derivatives which are said to be useful in the treatment of conditions such as thrombosis, ischaemic heart disease, stroke, transient ischaemic attack, migraine and the vascular complications of  
15 diabetes. There is no mention in the document of conditions mediated by the action of PGD<sub>2</sub> or other agonists at the CRTH2 receptor.

US 3,557,142 relates to 3-substituted-1-indole carboxylic acids and esters which are said to be useful in the treatment of inflammatory conditions.  
20

WO-A-03/097598 relates to compounds which are CRTH2 receptor antagonists. They do not have an aromatic substituent at the indole-3 position.

Cross *et al.*, *J. Med. Chem.* 29, 342-346 (1986) relates to a process for preparing  
25 indole-1-acetic acid derivatives from the corresponding esters. The compounds to which it relates are said to be inhibitors of thromboxane synthetase.

EP-A-0539117 relates to indole-1-acetic acid derivatives which are leukotriene antagonists  
30

US 2003/0153751 relates to indole-1-acetic acid derivatives which are sPLA<sub>2</sub>

inhibitors. However, all of the exemplified compounds have bulky substituents at the 2- and 5-positions of the indole system and are therefore very different from the compounds of the present invention.

- 5 US 2004/011648 discloses indole-1-acetic acid derivatives which are inhibitors of PAI-1. There is no suggestion that the compounds might have CRTH2 antagonist activity.

- 10 WO 2004/058164 relates to compounds which are said to be asthma and allergic inflammation modulators. The only compounds for which activity is demonstrated are entirely different in structure from the indole-1-acetic acid derivatives of the present invention.

- 15 Compounds which bind to the CRTH2 receptor are disclosed in WO-A-03/097042 and WO-A-03/097598. These compounds are indole acetic acids but in WO-A-03/097042 the indole system is fused at the 2-3 positions to a 5-7 membered carbocyclic ring. In WO-A-03/097598 there is a pyrrolidine group at the indole 3-position.

- 20 WO-A-03/101981, WO-A-03/101961 and WO-A-2004/007451 all relate to indole-1-acetic acid derivatives which are said to be CRTH2 antagonists but which differ in structure from the compounds of general formula (I) because there is no spacer or an -S- or -SO<sub>2</sub>- group at to the indole 3-position in place of the CH<sub>2</sub> group of the compounds of the present invention as described below.

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WO-A-2005/019171 also describes indole-1-acetic acid derivatives which are said to be CRTH2 antagonists and which are said to be useful for the treatment of various respiratory diseases. These compounds all have a substituent which is linked to the indole-3 position by an oxygen spacer.

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WO-A-2005/094816 again describes indole-1-acetic acid compounds, this time with

an aliphatic substituent at the 3-position of the indole ring. The compounds are said to be CRTH2 antagonists.

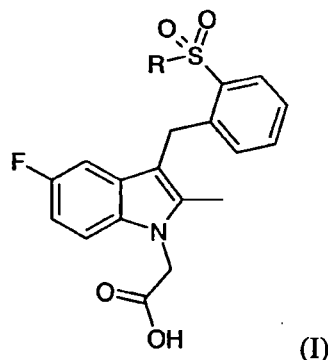
WO-A-2006/034419 relates to CRTH2 antagonist indole compounds which have a  
5 heterocyclic or heteroaromatic substituent directly linked to the 3-position of the indole ring system.

In our earlier application, WO-A-2005/044260, we describe compounds which are antagonists of PGD<sub>2</sub> at the CRTH2 receptor. These compounds are indole-1-acetic  
10 acid derivatives substituted at the 3-position with a group CR<sup>8</sup>R<sup>9</sup>, wherein R<sup>9</sup> is hydrogen or alkyl and R<sup>8</sup> is an aromatic moiety which may be substituted with one or more substituents. The compounds described in this document are potent antagonists *in vitro* of PGD<sub>2</sub> at the CRTH2 receptor. However, we have found that when tested *in vivo*, the pharmacokinetic profile of some compounds is not optimal and their  
15 potency in the whole blood eosinophil shape change test, which gives an indication of the likely *in vivo* activity of the compounds, is often somewhat less than might have been expected from the *in vitro* binding results.

Surprisingly, however, we have found that by making changes to the R<sup>8</sup> group of the  
20 compounds of WO-A-2005/044260 we are able to achieve improvements in the *in vitro* whole blood eosinophil shape change potency and the *in vivo* inhibition of DK-PGD<sub>2</sub>-induced blood eosinophilia and the pharmacokinetic profile on oral administration to a subject.

25 The present invention therefore relates to novel compounds which bind to CRTH2 and which are therefore useful in the treatment of diseases and conditions mediated by the activity of PGD<sub>2</sub> at the CRTH2 receptor.

In the present invention there is provided a compound of general formula (I)



wherein R is phenyl optionally substituted with one or more halo substituents;  
or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof.

- 5 The compounds of general formula (I) are antagonists at the CRTH2 receptor and are useful in the treatment of conditions which are mediated by PGD<sub>2</sub> or other agonists binding to CRTH2. These include allergic diseases, asthmatic conditions and inflammatory diseases, examples of which are asthma, including allergic asthma, bronchial asthma, exacerbations of asthma and related allergic diseases caused by
- 10 viral infection, particularly those exacerbations caused by rhinovirus and respiratory syncytial virus intrinsic, extrinsic, exercise-induced, drug-induced and dust-induced asthma, treatment of cough, including chronic cough associated with inflammatory and secretory conditions of the airways and iatrogenic cough, acute and chronic rhinitis, including rhinitis medicamentosa, vasomotor rhinitis, perennial allergic
- 15 rhinitis, seasonal allergic rhinitis, nasal polyposis, acute viral infection including common cold, infection due to respiratory syncytial virus, influenza, coronavirus and adenovirus, atopic dermatitis, contact hypersensitivity (including contact dermatitis), eczematous dermatitis, phyto dermatitis, photo dermatitis, seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosis et atrophica, pyoderma
- 20 gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme, cellulitis, panniculitis, cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; blepharitis
- 25 conjunctivitis, especially allergic conjunctivitis, anterior and posterior uveitis,

choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis; bronchitis, including infectious and eosinophilic bronchitis, emphysema, bronchiectasis, farmer's lung, hypersensitivity pneumonitis, idiopathic interstitial pneumonias, complications of lung transplantation, vasculitic and  
5 thrombotic disorders of the lung vasculature, pulmonary hypertension, food allergies, gingivitis, glossitis, periodontitis, oesophagitis including reflux, eosinophilic gastroenteritis, proctitis, pruritis ani, celiac disease, food-related allergies, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other CRTH2-mediated diseases, for example autoimmune diseases such as  
10 hyper IgE syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic psoriasis, antiphospholipid syndrome and systemic lupus erythematosus, AIDS, leprosy, Sezary syndrome, paraneoplastic syndrome, mixed and undifferentiated connective tissue diseases, inflammatory myopathies including dermatomyositis and  
15 polymyositis, polymyalgia rheumatica, juvenile arthritis, rheumatic fever, vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, temporal arteritis, myasthenia gravis, acute and chronic pain, neuropathic pain syndromes, neurodegeneration, central and peripheral nervous system complications of malignant, infectious or autoimmune  
20 processes, low back pain, familial Mediterranean Fever, Muckle-Wells syndrome, Familial Hibernian fever, Kikuchi disease, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, Still's disease, ankylosing spondylitis, reactive arthritis, undifferentiated spondyloarthritis, psoriatic arthritis, septic arthritis and other  
25 infection-related arthropathies and bone disorders and osteoarthritis; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, calcium phosphate related tendon syndrome and synovial inflammation, Behcet's disease, primary and secondary Sjogren's syndrome systemic sclerosis and limited scleroderma; hepatitis, cirrhosis of the liver, cholecystitis, pancreatitis, nephritis, nephritic syndrome, cystitis and Hunner's ulcer, acute and  
30 chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvo-vaginitis,

Peyronie's disease, erectile dysfunction, Alzheimer's disease and other dementing disorders; pericarditis, myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid, ischaemic reperfusion injuries, endocarditis, valvulitis, aortitis, phlebitis, thrombosis, treatment of common cancers and fibrotic conditions such as idiopathic pulmonary fibrosis including cryptogenic fibrosing alveolitis, keloids, excessive fibrotic scarring/adhesions post surgery, liver fibrosis including that associated with hepatitis B and C, uterine fibroids, sarcoidosis, including neurosarcoidosis, scleroderma, kidney fibrosis resulting from diabetes, fibrosis associated with RA, atherosclerosis, including cerebral atherosclerosis, vasculitis, myocardial fibrosis resulting from myocardial infarction, cystic fibrosis, restenosis, systemic sclerosis, Dupuytren's disease, fibrosis complicating anti-neoplastic therapy and chronic infection including tuberculosis and aspergillosis and other fungal infections, CNS fibrosis following stroke or the promotion of healing without fibrotic scarring.

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The compounds are particularly useful for the treatment or prevention of allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, eosinophilic bronchitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis, pain, neurodegenerative diseases and also other PGD<sub>2</sub>-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, psoriatic arthritis and osteoarthritis.

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The improved potency in the whole blood eosinophil shape change test and pharmacokinetic profile of the compounds of general formula (I) is particularly surprising since some of the compounds of WO-A-2005/044260, which are close in structure to the compounds of general formula (I) do not have these advantageous properties. In particular, the compound of Example 17 of WO-A-2005/044260 is

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similar to the compounds of the present invention and might have been expected to have similar properties. However, the replacement of the methylsulfonyl group at the 4-position of the benzene ring in Example 17 of WO-A-2005/044260 with the SO<sub>2</sub>R group at the 2-position of the benzene ring in the compounds of formula (I) has  
5 a significant effect on the pharmacokinetics and the activity of the compounds because when Compound 17 of WO-A-2005/044260 is administered orally, its pharmacokinetic profile *in vivo* is less favourable than that of the compounds of general formula (I).

10 In addition for many of the compounds of WO-A-2005/044260, we have found that their *in vitro* whole blood eosinophil shape change activity is often less than might have been expected from their *in vitro* activity as measured by radioligand binding experiments to the CRTH2 receptor.

15 Furthermore, the improvement in activity is very specific to the group of compounds of general formula (I) as compounds which are even more closely related than those of WO-A-2005/044260 do not have such favourable properties. For example, the analogues of general formula (I) in which the SO<sub>2</sub>R group is at the 3- or 4-position of the benzene ring are less active in *in vitro* whole blood eosinophil shape change tests.

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In the present specification "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a straight or branched saturated hydrocarbon chain having one to six carbon atoms and optionally substituted with one or more halo substituents or with one or more C<sub>3</sub>-C<sub>7</sub> cycloalkyl groups. Examples include methyl, ethyl, n-propyl, isopropyl, t-butyl, n-hexyl,  
25 trifluoromethyl, 2-chloroethyl, methylenecyclopropyl, methylenecyclobutyl, methylenecyclobutyl and methylenecyclopentyl.

"C<sub>1</sub>-C<sub>4</sub> alkyl" and "C<sub>1</sub>-C<sub>18</sub> alkyl" have similar meanings except that they contain from one to four and from one to eighteen carbon atoms respectively.

30 C<sub>3</sub>-C<sub>7</sub> cycloalkyl refers to a saturated 3 to 7 membered carbocyclic ring. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In the present specification, "halo" refers to fluoro, chloro, bromo or iodo.

The terms "aromatic moiety" and "aryl" in the context of the present specification  
5 refer to an aromatic ring system having from 5 to 14 ring carbon atoms and  
containing up to three rings. Examples of aromatic moieties are benzene and  
naphthalene. Aryl groups may be substituted with one or more substituents chosen  
from halo, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, a 5-7-membered heterocyclic ring or SO<sub>2</sub>R<sup>9</sup>  
where R<sup>9</sup> is as defined above.

10

Appropriate pharmaceutically and veterinarily acceptable salts of the compounds of  
general formulae (I) and (II) include basic addition salts such as sodium, potassium,  
calcium, aluminium, zinc, magnesium and other metal salts as well as choline,  
diethanolamine, ethanolamine, ethyl diamine and other well known basic addition  
15 salts.

Where appropriate, pharmaceutically or veterinarily acceptable salts may also  
include salts of organic acids, especially carboxylic acids, including but not limited  
to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate,  
20 pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate,  
cyclopentanoate, glucoheptanoate, glycerophosphate, oxalate, heptanoate, hexanoate,  
fumarate, nicotinate, pantoate, pectinate, 3-phenylpropionate, picrate, pivalate,  
propionate, tartrate, lactobionate, pivalate, camphorate, undecanoate and succinate,  
organic sulfonic acids such as methanesulfonate, ethanesulfonate, 2-hydroxyethane  
25 sulfonate, camphorsulfonate, 2-naphthalenesulfonate, benzenesulfonate, p-  
chlorobenzenesulfonate and p-toluenesulfonate; and inorganic acids such as  
hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, hemisulfate,  
thiocyanate, persulfate, phosphoric and sulfonic acids.

30 Salts which are not pharmaceutically or veterinarily acceptable may still be valuable  
as intermediates.

Prodrugs are any covalently bonded compounds which release the active parent drug according to general formula (I) *in vivo*. Examples of prodrugs include alkyl esters of the compounds of general formula (I), for example the esters of general formula (II) below.

If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein. Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

In the compounds of general formula (I), it is preferred that the phenyl group R is unsubstituted or is substituted with a single halo substituent, usually fluoro or chloro, which is generally at the 4-position of the phenyl group R.

Among the most preferred compounds are the following:

2-{5-Fluoro-2-methyl-3-[2-(phenylsulfonyl)benzyl]-1H-indol-1-yl}acetic acid;

2-{3-[2-(4-chlorophenylsulfonyl)benzyl]-5-fluoro-2-methyl-1H-indol-1-yl}acetic acid;

2-{5-Fluoro-3-[2-(4-fluorophenylsulfonyl)benzyl]-2-methyl-1H-indol-1-yl}acetic acid;

or the  $C_1$ - $C_6$  alkyl, aryl,  $(CH_2)_mOC(=O)C_1$ - $C_6$ alkyl,  $(CH_2)_mN(R^{11})_2$ ,

$CH((CH_2)_mO(C=O)R^{12})_2$  esters of any of the above; wherein

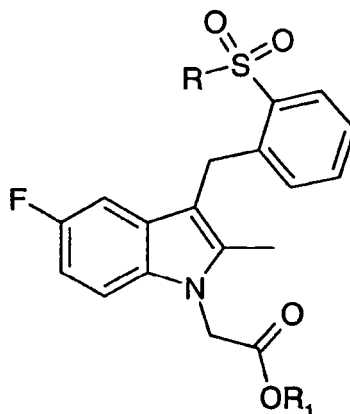
m is 1 or 2;

$R^{11}$  is hydrogen or methyl;

$R^{12}$  is  $C_1$ - $C_{18}$  alkyl.

In a further aspect of the present invention, there is provided a compound of general formula (II):

13



II

5 wherein R is as defined for general formula (I); and

$R^1$  is  $C_1$ - $C_6$  alkyl, aryl,  $(CH_2)_mOC(=O)C_1$ - $C_6$ alkyl,  $(CH_2)_mN(R^{11})_2$ ,  
 $CH((CH_2)_mO(C=O)R^{12})_2$ ;

m is 1 or 2;

$R^{11}$  is hydrogen or methyl;

10  $R^{12}$  is  $C_1$ - $C_{18}$  alkyl.

Compounds of general formula (II) are novel and may be used as prodrugs for  
 compounds of general formula (I). When the compound of general formula (II) acts  
 as a prodrug, it is later transformed to the drug by the action of an esterase in the  
 15 blood or in a tissue of the patient.

Examples of particularly suitable  $R^1$  groups when the compound of general formula  
 (II) is used as a prodrug include:

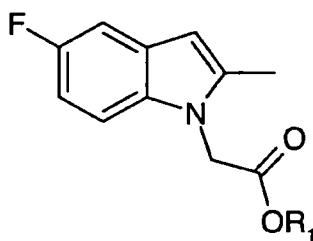
methyl, ethyl, propyl, phenyl,  $CH_2OC(=O)tBu$ ,  $CH_2CH_2N(Me)_2$ ,  $CH_2CH_2NH_2$  or  
 20  $CH(CH_2O(C=O)R^{12})_2$  wherein  $R^{12}$  is as defined above.

In addition to their use as prodrugs, compounds of formula (II) wherein  $R^1$  is  $C_1$ - $C_6$   
 alkyl may be used in a process for the preparation of a compound of general formula

(I), the process comprising reacting the compound of general formula (II) with a base such as sodium hydroxide or lithium hydroxide. The reaction may take place in an aqueous solvent or an organic solvent or a mixture of the two. A typical solvent used for the reaction is a mixture of tetrahydrofuran and water.

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Compounds of general formula (II) may be prepared from compounds of general formula (III):

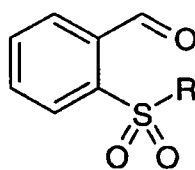


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III

wherein R<sup>1</sup> is as defined in general formula (II); by reaction with a compound of general formula (IV):

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(IV)

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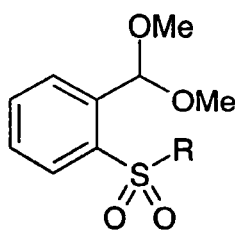
wherein R is as defined for general formula (I);  
under acidic reductive alkylation conditions.

Compounds of general formulae (III) are readily available or can be prepared by methods well known to those skilled in the art.

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Aldehydes of general formula (IV) can be prepared by deprotecting an acetal of general formula (V)

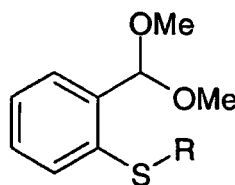
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(V)

10 wherein R is as defined for general formula (I). Deprotection may be achieved by reaction with an aqueous acid, for example sulphuric acid, followed by neutralisation with a base, typically solid potassium carbonate. The reaction may be carried out at 0 to 40°C, typically at room temperature.

15 Compounds of general formula (V) may be prepared by the oxidation of a compound of general formula (VI)



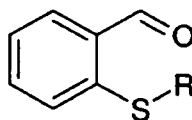
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(VI)

wherein R is as defined for general formula (I). The oxidation of the sulfide group can be achieved using an excess amount of an oxidising agent such as

chloroperoxybenzoic acid. The reaction mixture may be cooled initially, for example to -5 to 5°C and then allowed to warm, typically to room temperature.

5 An acetal of general formula (VI) may be prepared by protecting an aldehyde of general formula (VII)



10

(VII)

wherein R is as defined for general formula (I). The protection may be achieved by reaction with trimethylorthoformate and p-toluene sulfonic acid in dry conditions and  
15 under an inert atmosphere followed by sodium methoxide in methanol.

Compounds of general formula (VII) are commercially available. Alternatively, they can be prepared by reacting a compound of general formula (VIII):

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R-SH

(VIII)

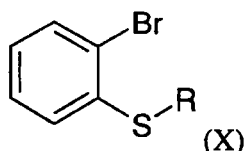
where R is as defined for general formula (I) with 2-fluorobenzaldehyde. The reaction may be carried out under mildly basic conditions in a polar solvent such as DMSO and under an inert atmosphere at a temperature of from 80 to 110°C.

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Compounds of general formula (VIII) are commercially available or may be prepared by methods well known to those of skill in the art.

Another route to compounds of general formula (VII) as defined above is *via* the

formylation of a compound of general formula (X):

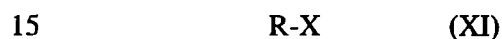


where R is as defined for general formula (I);

- 5 using *n*-butyl lithium and dimethylformamide (DMF) in an organic solvent such as tetrahydrofuran.

Typically, the reaction is carried out under an inert atmosphere, for example nitrogen, cooled to a temperature of about -78°C while reacting with the *n*-butyl  
10 lithium and allowed to warm to room temperature after the addition of the DMF.

Compounds of general formula (X) may be prepared by reacting 2-bromothiophenol with a compound of general formula (XI):



Where R is as defined for general formula (I) and X is a leaving group, particularly a halo group such as chloro or bromo.

- 20 The reaction may be carried out in the presence of a base, for example caesium carbonate and at a temperature of 20-50°C, typically 40°C.

An alternative route to compounds of general formula (IV) is by reaction of sodium salts of general formula (IX):

25



wherein R is as defined for general formula (I) with 2-fluorobenzaldehyde. The reaction may be carried out in a solvent such as dimethylsulfoxide at elevated

temperature, typically 80 to 110°C. The reaction may take several days to go to completion.

Sodium salts of general formula (IX) are commercially available.

5

Compounds of general formula (IV) may also be prepared directly from compounds of general formula (VII) without the need for the protection and deprotection steps. In this procedure a cooled oxidising agent such as *meta* chloroperoxybenzoic acid may be added to the compound of general formula (VII), typically with cooling to  
10 about -5 to 5°C. The reaction mixture may be allowed to warm to 15 to 30°C, usually room temperature, and then reacted with sodium metabisulfite.

As mentioned above, some compounds of general formula (VII) are commercially available.

15

Compounds of general formula (I) are CRTH2 receptor antagonists and compounds of general formula (II) are prodrugs for compounds of general formula (I). Compounds of general formulae (I) and (II) are therefore useful in a method for the treatment of diseases and conditions mediated by PGD<sub>2</sub> or other agonists at the  
20 CRTH2 receptor, the method comprising administering to a patient in need of such treatment a suitable amount of a compound of general formula (I) or (II).

In a third aspect of the invention, there is provided a compound of general formula (I) or (II) for use in medicine, particularly for use in the treatment or prevention of  
25 diseases and conditions mediated by PGD<sub>2</sub> or other CRTH2 receptor agonists.

Furthermore, there is also provided the use of a compound of general formula (I) or (II) in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by CRTH2 receptor agonists, particularly PGD<sub>2</sub>.

30

As mentioned above, such diseases and conditions include allergic diseases,

asthmatic conditions and inflammatory diseases, examples of which are asthma, including allergic asthma, bronchial asthma, intrinsic, extrinsic, exercise-induced, drug-induced and dust-induced asthma, treatment of cough, including chronic cough associated with inflammatory and secretory conditions of the airways and iatrogenic

5 cough, acute and chronic rhinitis, including rhinitis medicamentosa, vasomotor rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis, nasal polyposis, acute viral infection including common cold, infection due to respiratory syncytial virus, influenza, coronavirus and adenovirus, atopic dermatitis, contact hypersensitivity (including contact dermatitis), eczematous dermatitis, phyto dermatitis, photo

10 dermatitis, seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosis et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema

15 multiforme, cellulitis, panniculitis, cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; blepharitis conjunctivitis, especially allergic conjunctivitis, anterior and posterior uveitis, choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis; bronchitis, including infectious and eosinophilic bronchitis, emphysema, bronchiectasis, farmer's lung,

20 hypersensitivity pneumonitis, idiopathic interstitial pneumonias, complications of lung transplantation, vasculitic and thrombotic disorders of the lung vasculature, pulmonary hypertension, food allergies, gingivitis, glossitis, periodontitis, oesophagitis including reflux, eosinophilic gastroenteritis, proctitis, pruritis ani, celiac disease, food-related allergies, inflammatory bowel disease, ulcerative colitis and

25 Crohn's disease, mastocytosis and also other CRTH2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic psoriasis, antiphospholipid syndrome and systemic lupus erythematosus, AIDS, leprosy, Sezary syndrome, paraneoplastic syndrome, mixed

30 and undifferentiated connective tissue diseases, inflammatory myopathies including dermatomyositis and polymyositis, polymyalgia rheumatica, juvenile arthritis,

rheumatic fever, vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, temporal arteritis, myasthenia gravis, acute and chronic pain, neuropathic pain syndromes, neurodegeneration, central and peripheral nervous system complications of malignant, infectious or autoimmune processes, low back pain, familial Mediterranean Fever, Muckle-Wells syndrome, Familial Hibernian fever, Kikuchi disease, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, Still's disease, ankylosing spondylitis, reactive arthritis, undifferentiated spondyloarthritis, psoriatic arthritis, septic arthritis and other infection-related arthropathies and bone disorders and osteoarthritis; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, calcium phosphate related tendon syndrome and synovial inflammation, Behcet's disease, primary and secondary Sjogren's syndrome systemic sclerosis and limited scleroderma; hepatitis, cirrhosis of the liver, cholecystitis, pancreatitis, nephritis, nephritic syndrome, cystitis and Hunner's ulcer, acute and chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvovaginitis, Peyronie's disease, erectile dysfunction, Alzheimer's disease and other dementing disorders; pericarditis, myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid, ischaemic reperfusion injuries, endocarditis, valvulitis, aortitis, phlebitis, thrombosis, treatment of common cancers and fibrotic conditions such as idiopathic pulmonary fibrosis including cryptogenic fibrosing alveolitis, keloids, excessive fibrotic scarring/adhesions post surgery, liver fibrosis including that associated with hepatitis B and C, uterine fibroids, sarcoidosis, including neurosarcoidosis, scleroderma, kidney fibrosis resulting from diabetes, fibrosis associated with RA, atherosclerosis, including cerebral atherosclerosis, vasculitis, myocardial fibrosis resulting from myocardial infarction, cystic fibrosis, restenosis, systemic sclerosis, Dupuytren's disease, fibrosis complicating anti-neoplastic therapy and chronic infection including tuberculosis and aspergillosis and other fungal infections, and CNS fibrosis following stroke. The compounds are also of use in the promotion of healing without fibrotic scarring.

The compounds of general formula (I) or (II) must be formulated in an appropriate manner depending upon the diseases or conditions they are required to treat.

Therefore, in a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of general formula (I) or (II) together with a pharmaceutical excipient or carrier. Other active materials may also be present, as may be considered appropriate or advisable for the disease or condition being treated or prevented.

10 The carrier, or, if more than one be present, each of the carriers, must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient.

The formulations include those suitable for oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration and may be prepared by any methods well known in the art of pharmacy.

20 The route of administration will depend upon the condition to be treated but preferred compositions are formulated for oral, nasal, bronchial or topical administration.

The composition may be prepared by bringing into association the above defined active agent with the carrier. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product. The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of general formula (I) or (II) in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

30

Formulations for oral administration in the present invention may be presented as:

discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active agent; as a powder or granules; as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water in oil liquid emulsion; or as a bolus etc.

5

For compositions for oral administration (e.g. tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e.g. binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose,  
10 hydroxypropylmethylcellulose, sucrose and starch; fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid; and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica. Flavouring agents  
15 such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art.

A tablet may be made by compression or moulding, optionally with one or more  
20 accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert  
25 liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent.

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles  
30 comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active agent in a suitable liquid carrier.

For topical application to the skin, compounds of general formula (I) or (II) may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceuticals such as the British Pharmacopoeia.

Compounds of general formula (I) or (II) may be used for the treatment of the respiratory tract by nasal, bronchial or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Parenteral formulations will generally be sterile.

Typically, the dose of the compound will be about 0.01 to 100 mg/kg; so as to maintain the concentration of drug in the plasma at a concentration effective to inhibit PGD<sub>2</sub> at the CRTH2 receptor. The precise amount of a compound of general formula (I) or (II) which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

Compounds of general formula (I) or (II) may be used in combination with one or

more active agents which are useful in the treatment of the diseases and conditions listed above, although these active agents are not necessarily inhibitors of PGD<sub>2</sub> at the CRTH2 receptor.

- 5 Therefore, the pharmaceutical composition described above may additionally contain one or more of these active agents.

- There is also provided the use of a compound of general formula (I) or (II) in the preparation of an agent for the treatment of diseases and conditions mediated by  
10 CRTH2 receptor agonists, especially PGD<sub>2</sub>, wherein the agent also comprises an additional active agent useful for the treatment of the same diseases and conditions.

- These additional active agents may be other CRTH2 receptor antagonists or may have a completely different mode of action. They include existing therapies for  
15 allergic and other inflammatory diseases including:

Suplatast tosylate and similar compounds;

$\beta_1$  to  $\beta_4$  adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate and pirbuterol or methylxanthanines such as theophylline and

- 20 aminophylline, mast cell stabilisers such as sodium cromoglycate or muscarinic receptor (M1, M2 or M4) antagonists;

antihistamines, for example histamine H<sub>1</sub> receptor antagonists such as loratidine cetirizine, desloratidine, fexofenadine, astemizole, azelastine and chlorpheniramine or histamine H<sub>2</sub> or H<sub>4</sub> receptor antagonists;

- 25  $\alpha_1$  and  $\alpha_2$  adrenoreceptor agonists such as propylhexedrine phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride and ethylnorepinephrine hydrochloride;

insulin-like growth factor (IGF-1) mimetics;

- 30 matrix metalloprotease (MMP) inhibitors, for example inhibitors of stromelysins, collagenases gelatinases and aggrecanase, especially collagenase-1, collagenase-2,

- collagenase-3, stromelysin-1, stromelysin-2, stromelysin-3 and MMP-12;  
modulators of chemokine receptor function, for example CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family) or CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX<sub>3</sub>CR1 for the C-X<sub>3</sub>-C family;  
5 antiviral agents such as Viracept, AZT, acyclovir and famciclovir and antiseptics compounds such as Valant;  
cardiovascular agents, for example calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, ACE inhibitors, Angiotensin-2 receptor  
10 antagonists and platelet aggregation inhibitors;  
CNS agents, for example antidepressants such as sertraline, anti-Parkinsonian drugs such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine antagonists, Dopamine agonists and  
15 inhibitors of neuronal nitric oxide synthase and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate;  
Tryptase inhibitors;  
Platelet activating factor (PAF) antagonists;  
Interleukin converting enzyme (ICE) inhibitors;  
20 IMPDH inhibitors;  
Adhesion molecule inhibitors including VLA-4 antagonists;  
Cathepsins;  
MAP kinase inhibitors;  
Glucose-6-phosphonate dehydrogenase inhibitors;  
25 Kinin-B<sub>1</sub> and B<sub>2</sub> receptor antagonists;  
Anti-gout agents such as colchicine;  
Xanthine oxidase inhibitors such as allopurinol;  
Uricosuric agents, such as probenecid, dulfenpyrazone and benzbromarone;  
Growth hormone secretagogues;  
30 Transforming growth factor beta (TGFβ);  
Platelet-derived growth factor (PDGF)

- Fibroblast growth factor e.g. basic fibroblast growth factor  
 Granulocyte macrophage colony stimulating factor (GM-CSF);  
 Capsaicin;  
 Tachykinin NK<sub>1</sub> and NK<sub>3</sub> receptor antagonists such as NKP-608C, talnetant and D-  
 5 4418;  
 Elastase inhibitors such as UT-77 and ZD-0892;  
 Induced nitric oxide synthase inhibitors (iNOS);  
 Osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax;  
 anticholinergic agents such as ipratropium bromide, tiotropium bromide, oxitropium  
 10 bromide, pirenzepine and telenzepine;  
 leukotriene antagonists (LTB<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> antagonists) such as phenothiazine-3-  
 ones such as L-651,392, amidino compounds such as CGS-25019c, benzoxalamines  
 such as ontazolast, benzene carboximidamides such as BIIL 284/260 and compounds  
 such as zafirlukast, ablukast, montelukast, pranlukast, verlukast, RG-12525, Ro-  
 15 245913, iralukast and BAY x 7195;  
 leukotriene biosynthesis inhibitors such as 5-lipoxygenase inhibitors or 5-  
 lipoxygenase activating protein (FLAP) inhibitors such as zileuton, ABT-761,  
 fenleuton, tepoxalin, Abbott-79175, N-(5-substituted)-thiophene-2-  
 alkylsulfonamides, 2,6-di-tert-butylphenol hydrazones, methoxytetrahydropyrans  
 20 such as ZD2138, SB-210661, pyridinyl-substituted-2-cyanonaphthalene compounds  
 such as L-739010, 2-cyanoquinoline compounds such as L-746,530, indole and  
 quinoline compounds such as MK-591, MK-886 and BAY x 1005;  
 Phosphodiesterase inhibitors, including PDE4 inhibitors such as PDE4D inhibitors;  
 anti-IgE antibody therapies such as omalizumab;  
 25 anti-infectives such as fusidic acid (particularly for the treatment of atopic  
 dermatitis);  
 anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis);  
 immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of  
 inflammatory skin disease or alternatively FK-506, rapamycin, cyclosporine,  
 30 azathioprine or methotrexate;  
 antiproliferative/antineoplastic drugs such as alkylating agents, e.g. cisplatin,

- carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas, antimetabolites, e.g. antifolates such as fluoropyrimidines such as 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel;
- 5 antitumour antibiotics such as anthracyclines such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and methramycin;
- antimitotic agents such as vinca alkaloids including vincristine, vinblastine, vindesine and vinorelbine and taxoides such as taxol and taxostere and
- 10 topoisomerase inhibitors such as epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin; cytostatic agents such as antioestrogens such as tamoxifen, toremifene, raloxifene, droloxifene and idoxifene, oestrogen receptor down regulators such as fulvestrant, antiandrogens such as bicalutamide, flutamide, nilutamide and cyproterone acetate, LHRH antagonists or agonists such as goserelin,
- 15 leuprorelin and buserelin, progestogens such as megestrol acetate, aromatase inhibitors such as anastrozole, letrozole, borazole and exemestane and inhibitors of 5 $\alpha$  reductase such as finasteride;
- agents which inhibit cancer cell invasion, for example metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor
- 20 function;
- inhibitors of growth factor function for example growth factor antibodies, growth factor receptor antibodies, e.g. the anti-erbB2 antibody trastuzumab and the anti-erbB1 antibody cetuximab, farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine or threonine kinase inhibitors, for example inhibitors of the epidermal
- 25 growth factor family such as EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033), or inhibitors of the platelet derived
- 30 growth factor or the hepatocyte growth factor families;
- antiangiogenic agents, particularly those which inhibit the effects of vascular

- endothelial growth factor e.g. the anti-vascular endothelial cell growth factor antibody bevacizumab and also compounds that work by other mechanisms e.g. linomide, inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin; vascular damaging agents such as Combretastatin A4;
- 5 antisense therapies such as those which are directed to targets listed above, e.g. ISIS 2503, an anti-ras antisense;
- gene therapy agents, including agents for replacing aberrant genes such as aberrant p53, or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy), cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme
- 10 or agents for increasing patient tolerance to chemotherapy or radiotherapy such as multi-drug resistant gene therapy;
- immunotherapy agents including *in vivo* and *ex vivo* approaches to increase the immunogenicity of patient tumour cells such as transfection with cytokines such as IL2, IL4 or GM-CSF, approaches to decrease T-cell anergy, approaches using
- 15 transfected immune cells such as cytokine-transfected dendritic cells or approaches using cytokine-transfected tumour cell lines or anti-idiotypic antibodies;
- corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate and mometasone furoate and hyaluronic acids such as hyalgan and synvisc and P2X7
- 20 receptor antagonists;
- drugs which promote Th1 cytokine response such as interferons, TNF or GM-CSF. CRTH2 antagonists may also be combined with:
- other antagonists of PGD<sub>2</sub> acting at other receptors such as DP antagonists; inhibitors of phosphodiesterase type 4 such as cilostazol;
- 25 drugs that modulate cytokine production such as inhibitors of TNF $\alpha$  converting enzyme (TACE) anti-TNF monoclonal antibodies, TNF receptor immunoglobulin molecules, inhibitors of other TNF isoforms, non-selective COX-1/COX-2 inhibitors such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid,
- 30 indomethacin, sulindac and apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin; COX-2 inhibitors such as meloxicam, celecoxib, fofecoxib,

valdecoxib and etoricoxib, low dose methotrexate, lefunomide, ciclesonide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold. drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors;

- 5 PPAR- $\gamma$  agonists such as rosiglitazone; or with anti-RSV antibodies such as Synagis (palivizumab) and agents that may be used to treat rhinovirus infection in the future e.g. interferon-beta and other interferons

- In yet a further aspect of the invention, there is provided a product comprising a  
10 compound of general formula (I) or (II) and one or more of the agents listed above as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD<sub>2</sub> at the CRTH2 receptor.

- The invention will now be described in greater detail with reference to the following  
15 non limiting examples and the drawings in which:

FIGURE 1 is a plot of blood concentration of Compound 1 versus time for rats dosed orally with 3mg/kg of Compound 1.

- 20 FIGURE 2 is a plot of blood concentration of Compound 2 versus time for rats dosed orally with 3mg/kg of Compound 2.

FIGURE 3 is a plot of blood concentration of Compound 3 versus time for rats dosed orally with 3mg/kg of Compound 3.

- 25 FIGURE 4 is a plot of blood concentration of Comparator Compound A versus time for rats dosed orally with 3mg/kg of Compound A.

- FIGURE 5 is a plot of blood concentration of Comparator Compound B versus time  
30 for rats dosed orally with 3mg/kg of Compound B.

FIGURE 6 shows the effect of doses of 0.0001, 0.001, 0.01 and 0.1  $\mu\text{g/kg}$  of Compound 1 on DK-PGD<sub>2</sub> induced eosinophilia in rats.

FIGURE 7 shows the effect of doses of 0.001, 0.01, 0.1 and 1.0  $\mu\text{g/kg}$  of Compound 2 on DK-PGD<sub>2</sub> induced eosinophilia in rats.

FIGURE 8 shows the effect of doses of 0.001, 0.01, 0.1 and 1.0  $\mu\text{g/kg}$  of Compound 3 on DK-PGD<sub>2</sub> induced eosinophilia in rats.

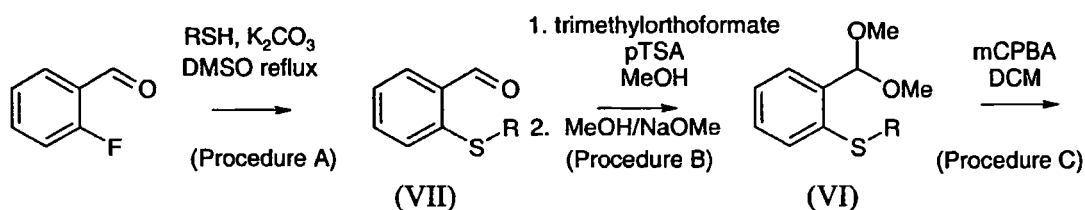
FIGURE 9 shows the effect of doses of 0.01, 0.1 and 1.0 mg/kg of Compound A on DK-PGD<sub>2</sub> induced eosinophilia in rats.

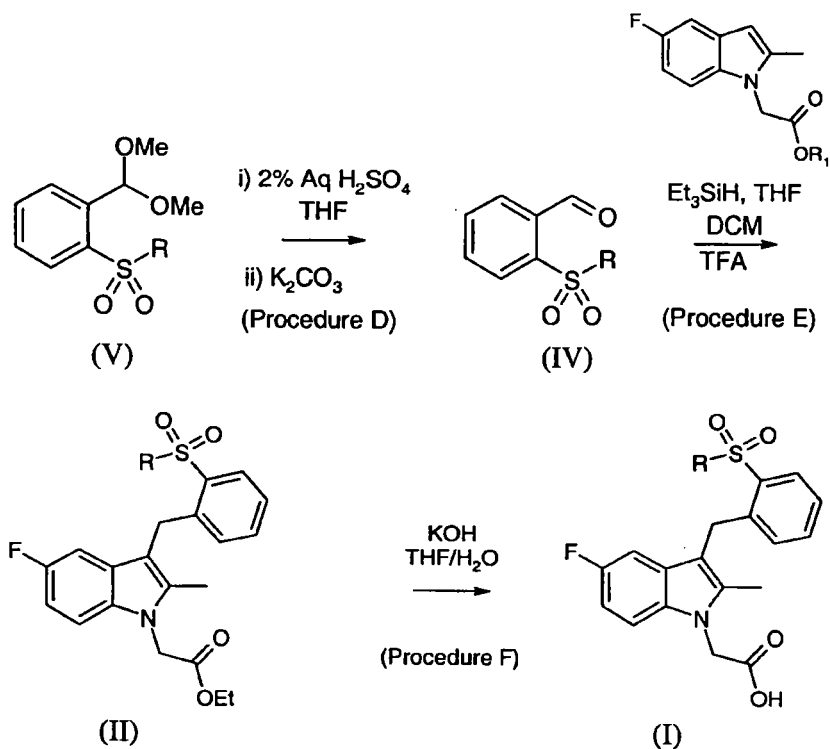
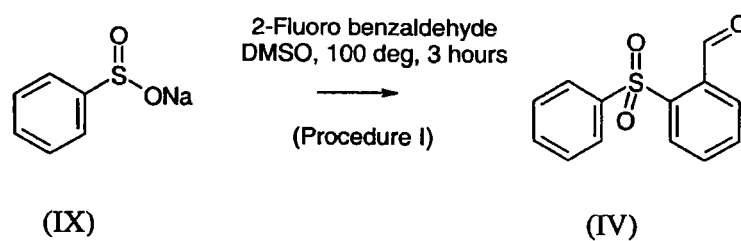
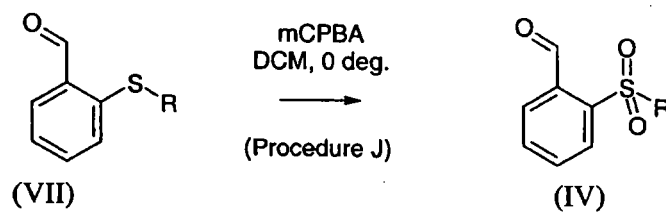
FIGURE 10 shows the effect of doses of 0.001, 0.01, 0.1 and 1.0 mg/kg of Compound B on DK-PGD<sub>2</sub> induced eosinophilia in rats.

### Preparation of Compounds of General Formula I

The compounds of Examples 1 to 3 were prepared according to the following reaction schemes.

#### Scheme 1



Scheme 2Scheme 3

**Example 1 – Preparation of 2-(5-fluoro-2-methyl-3-(2-(phenylsulfonyl)benzyl)-1H-indol-1-yl)acetic acid (Compound 1)**

From commercial benzenesulfinic acid sodium salt and 2-fluorobenzaldehyde.

5     **a)     Procedure I. ( $S_NAr$ ) to yield 2-(phenylsulfonyl)benzaldehyde**

To a solution of 2-fluoro benzaldehyde (5.00 ml, 47.6 mmol) in dimethyl sulfoxide (45 ml) was added benzene sulfinic acid sodium salt (8.60 g, 52.4 mmol) and the resulting mixture heated to 100 °C. Upon heating the sulfinic acid salt dissolved. The solution was heated at 100 °C for 3 days. The reaction was cooled to room  
10    temperature and water (50 ml) added. This mixture was extracted with ethyl acetate, the combined organic extracts were washed with saturated brine, dried over  $MgSO_4$  and concentrated in vacuo. The crude material was purified by flash chromatography on silica eluting with 25 % ethyl acetate : petroleum ether (40 – 60 °C) to 33 % ethyl acetate : petroleum ether (40 – 60 °C) to give (4.12 g, 16.7 mmol, 35 %).  $\delta_H$  (300  
15    MHz,  $d_6$ -DMSO) 10.68 (1H, s, CHO), 8.26-8.17 (1H, m, Ar), 8.08-7.99 (2H, m, Ar), 7.99-7.89 (3H, m, Ar) and 7.80-7.62 (3H, m, Ar).

20    **b)     Procedure E. (Reductive alkylation) to yield ethyl 2-(5-fluoro-2-methyl-3-(2-(phenylsulfonyl)benzyl)-1H-indol-1-yl)acetate**

To a solution of 2(5-fluoro-2-methyl-1H-indol-1-yl)acetic acid (1.29 g, 1.49 mmol), 2-(phenylsulfonyl)benzaldehyde (1.50 g, 6.10 mmol) and triethylsilane (4.30 ml, 27.0 mmol) in dichloromethane (40 ml) was added trifluoroacetic acid (1.25 ml, 16.5 mmol) dropwise under  $N_2$  at 0 °C over 30 minutes. The reaction was warmed to  
25    room temperature and stirred for 2 hours. Saturated aqueous sodium hydrogen carbonate solution was added and the product extracted with dichloromethane. The combined organic extracts were washed with saturated brine, dried over  $MgSO_4$  and concentrated in vacuo giving a brown oil which was triturated with petroleum ether (40 – 60 °C) to give a white solid (1.34 g, 2.88 mmol 52%).  
30     $\delta_H$  (300 MHz,  $CDCl_3$ ) 8.36-8.30 (1H, m, Ar), 8.00-7.93 (2H, m, Ar), 7.68-7.52 (3H, m, Ar), 7.45-7.33 (2H, m, Ar), 7.05 (1H, dd,  $J$  8.6 and 4.3 Hz, Ar), 6.96-6.90 (1H, m,

Ar), 6.82 (1H, td, *J* 9.1 and 2.7Hz, Ar), 6.24 (1H, dd, *J* 9.5 and 2.4Hz, Ar), 4.76 (2H, s, NCH<sub>2</sub>), 4.22 (2H, s, ArCH<sub>2</sub>Ar), 4.21 (2H, q, *J* 7.1Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.14 (3H, s, CH<sub>3</sub>) and 1.27 (3H, t, *J* 7.1Hz, CH<sub>2</sub>CH<sub>3</sub>).

5    **c)    Procedure F (Saponification) to yield 2-(5-fluoro-2-methyl-3-(2-(phenylsulfonyl)benzyl)-1H-indol-1-yl)acetic acid**

To a stirred solution of ester product of step (b) (1.33 g, 2.86 mmol) in tetrahydrofuran (15 ml) was added a solution of aqueous KOH (500 mg, 8.57 mmol) in water (15 ml). After 2 hours the tetrahydrofuran was removed under reduced  
10    pressure and the basic aqueous layer was washed with ethyl acetate. The remaining aqueous layer was acidified with HCl (2N) and extracted with ethyl acetate. The combined organic extracts were washed with saturated brine, dried over MgSO<sub>4</sub> and concentrated in vacuo giving a brown solid which was triturated with a mixture of diethyl ether and petroleum ether (40 – 60 °C) to give white solid (1.14 g, 2.61 mmol  
15    91%).

$\delta_{\text{H}}$  (300 MHz, *d*<sub>6</sub>-DMSO) 13.00 (1H, bs, CO<sub>2</sub>H), 8.26-8.20 (1H, m, Ar), 7.99-7.93 (2H, m, Ar), 7.80-7.62 (3H, m, Ar), 7.55-7.48 (2H, m, Ar), 7.34 (1H, dd, *J* 8.6 and 4.3Hz, Ar), 6.93-6.87 (1H, m, Ar), 6.81 (1H, td, *J* 9.1 and 2.7Hz, Ar), 6.18 (1H, dd, *J* 9.7 and 2.4Hz, Ar), 4.95 (2H, s, NCH<sub>2</sub>), 4.14 (2H, s, ArCH<sub>2</sub>Ar) and 2.06 (3H, s, CH<sub>3</sub>). Tr = 4.62 min (95%), *m/z* (M+H)<sup>+</sup> 438.3.  
20

**Example 2 – Preparation of 2-(3-(2-(4-chlorophenylsulfonyl)benzyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic acid (Compound 2)**

From commercial 2-(4-chlorophenylthio)benzaldehyde.

5     **a)     Procedure J. (Direct Oxidation) to yield 2-(4-chlorophenylsulfonyl)benzaldehyde**

To a solution of 2-(4-chlorophenylthio)benzaldehyde (2.00 g, 8.00 mmol) in dichloromethane (20mL) at 0 °C was added *meta* chloroperoxybenzoic acid (77% max, 5.40 g, 24.17 mmol) in portions over 15 minutes, then warmed to room  
10     temperature and stirred for 2 hours. Aqueous sodium metabisulfite solution was added carefully until effervescence ceased. This solution was extracted with dichloromethane and the combined organic extracts were washed with NaOH (1N) then saturated brine, dried over MgSO<sub>4</sub> and concentrated in vacuo giving a white solid (1.05 g, 3.74 mmol, 46 %).  $\delta_H$  (300 MHz, *d*<sub>6</sub>-DMSO) 10.69 (1H, s, CHO), 8.25-  
15     8.18 (1H, m, Ar), 8.07-8.00 (2H, m, Ar), 8.00-7.90 (3H, m, Ar) and 7.81-7.64 (3H, m, Ar).

b)     **Procedure E. (Reductive alkylation) to yield ethyl 2-(3-(2-(4-chlorophenylsulfonyl)benzyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetate**  
20      $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 8.33-8.26 (1H, m, Ar), 7.89-7.82 (2H, m, Ar), 7.53-7.46 (2H, m, Ar), 7.44-7.73 (2H, m, Ar), 7.06 (1H, dd, *J* 8.6 and 4.3Hz, Ar), 7.02-6.96 (1H, m, Ar), 6.84 (1H, td, *J* 9.1 and 2.7Hz, Ar), 6.33 (1H, dd, *J* 9.5 and 2.4Hz, Ar), 4.76 (2H, s, NCH<sub>2</sub>), 4.23 (2H, s, ArCH<sub>2</sub>Ar), 4.22 (2H, q, *J* 7.2Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.16 (3H, s, CH<sub>3</sub>) and 1.27 (3H, t, *J* 7.2Hz, CH<sub>2</sub>CH<sub>3</sub>).

25

c)     **Procedure F. (Saponification) to yield 2-(3-(2-(4-chlorophenylsulfonyl)benzyl)-5-fluoro-2-methyl-1H-indol-1-yl)acetic acid**  
 $\delta_H$  (300 MHz, *d*<sub>6</sub>-DMSO) 13.01 (1H, bs, CO<sub>2</sub>H), 8.27-8.20 (1H, m, Ar), 7.97-7.90 (2H, m, Ar), 7.74-7.67 (2H, m, Ar), 7.57-7.51 (2H, m, Ar), 7.34 (1H, dd, *J* 8.7 and  
30     4.3Hz, Ar), 7.00-6.93 (1H, m, Ar), 6.81 (1H, td, *J* 9.4 and 2.6Hz, Ar), 6.16 (1H, dd, *J*

9.8 and 2.6Hz, Ar), 4.95 (2H, s, NCH<sub>2</sub>), 4.17 (2H, s, ArCH<sub>2</sub>Ar) and 2.12 (3H, s, CH<sub>3</sub>). Tr = 4.04 min (96%), *m/z* (M+H)<sup>+</sup> 472.0.

**Example 3 – Preparation of 2-(5-fluoro-3-(2-(4-fluorophenylsulfonyl)benzyl)-2-methyl-1H-indol-1-yl)acetic acid (Compound 3)**

**a) Procedure A. (S<sub>N</sub>Ar) to yield 2-(4-fluorophenylthio)benzaldehyde**

To a suspension of 4-fluorophenylthiol (0.86 ml, 8.06 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.50 g, 18.12 mmol) in DMSO (5 ml) was added 2-fluorobenzaldehyde (1.00 g, 8.06 mmol) under N<sub>2</sub> and the mixture heated at 100 °C for 3 hours. The reaction was cooled to room temperature and water (20 ml) added. This mixture was extracted with ethyl acetate, the combined organic extracts were washed with saturated brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a yellow solid (1.20 g, 5.17 mmol, 64%)  
δ<sub>H</sub> (300 MHz, *d*<sub>6</sub>-DMSO) 10.23 (1H, s, CHO), 7.98 (1H, dd, *J* 7.3 and 1.7Hz, Ar), 7.63-7.49 (3H, m, Ar), 7.45-7.32 (3H, m, Ar) and 6.88 (1H, d, *J* 7.7Hz, Ar).

**b) Procedure B. (Aldehyde Protection) to yield (2-(dimethoxymethyl)phenyl)(4-fluorophenyl)sulfane**

To a solution of the aldehyde product of step (a) (1.20 g, 5.17 mmol) and trimethylorthoformate (0.62 ml, 0.58 mmol) in anhydrous methanol (80 ml) was added *p*-toluenesulfonic acid (0.10 g, 0.58 mmol) under N<sub>2</sub> and the mixture stirred at room temperature for 72 hours. A solution of sodium methoxide in methanol (0.12 ml, 25 % sol, 0.58 mmol) was added and all solvent removed *in vacuo* giving a colourless oil (1.50 g). No further purification was carried out.  
δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 7.64 (1H, dd, *J* 7.3 and 2.0Hz, Ar), 7.38-7.30 (2H, m, Ar), 7.29-7.19 (2H, m, Ar), 7.15-7.10 (1H, m, Ar), 7.07-6.99 (2H, m, Ar), 5.72 (1H, s, CH(CH<sub>3</sub>)<sub>2</sub>) and 3.37 (6H, s, CH(CH<sub>3</sub>)<sub>2</sub>).

**c) Procedure C. (Oxidation) to yield 1-(dimethoxymethyl)-2-(4-fluorophenylsulfonyl)benzene**

To a solution of the sulfide product of step (b) (1.50 g) in dichloromethane (40 ml) was added 3-chloroperoxybenzoic acid (4.60 g, 20.59 mmol) portionwise over 30 minutes at 0 °C. The reaction was warmed to room temperature and stirred for 2 hours. Aqueous sodium metabisulfite solution (50 ml) was added and the product extracted with dichloromethane. The combined organic extracts were washed with NaOH (50 ml, 1N) followed by saturated brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a yellow oil (1.40 g, 4.52 mmol 87 % over 2 steps).

10  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 8.11 (1H, dd, *J* 8.1 and 1.5Hz, Ar), 7.85 (2H, dd, *J* 8.9 and 5.0Hz Ar), 7.76 (1H, dd, *J* 7.9 and 1.5Hz, Ar), 7.58 (1H, ddd *J* 7.8, 7.6 and 1.4Hz, Ar), 7.47 (1H, ddd *J* 7.8, 7.6 and 1.4Hz, Ar), 7.14-7.05 (2H, m, Ar), 6.12 (1H, s, CH(CH<sub>3</sub>)<sub>2</sub>) and 3.12 (6H, s, CH(CH<sub>3</sub>)<sub>2</sub>).

15 **d) Procedure D. (Acetal deprotection) to yield 2-(4-fluorophenylsulfonyl)benzaldehyde**

To a solution of 1-(dimethoxymethyl)-2-(4-fluorophenylsulfonyl)benzene (1.40 g, 4.52 mmol) in tetrahydrofuran (20 ml) was added aqueous sulphuric acid (20 ml, 2 % solution) and stirred at room temperature for 12 hours. Solid K<sub>2</sub>CO<sub>3</sub> was added until effervescence ceased and the solution was basic. The solution was extracted with ethyl acetate, the combined organic extracts were washed with saturated brine, dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a yellow solid (0.90 g, 340 mmol 75 %).

20  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 10.85 (1H, s, CHO), 8.21-8.16 (1H, m, Ar), 8.08-8.02 (1H, m, Ar), 7.97-7.90 (2H, m, Ar), 7.80-7.74 (2H, m, Ar) and 7.27-7.19 (2H, m, Ar).

**e) Procedure E. (Reductive alkylation) to yield ethyl 2-(5-fluoro-3-(2-(4-fluorophenylsulfonyl)benzyl)-2-methyl-1H-indol-1-yl)acetate**

30  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 8.32-8.26 (1H, m, Ar), 8.00-7.90 (2H, m, Ar), 7.43-7.37 (2H, m, Ar), 7.26-7.17 (2H, m, Ar), 7.06 (1H, dd, *J* 8.8 and 4.3Hz, Ar), 7.00-6.94 (1H, m, Ar), 6.84 (1H, td, *J* 9.1 and 2.6Hz, Ar), 6.32 (1H, dd, *J* 9.5 and 2.6Hz, Ar), 4.77 (2H,

s, NCH<sub>2</sub>), 4.24 (2H, s, ArCH<sub>2</sub>Ar), 4.22 (2H, q, *J* 7.2Hz, CH<sub>2</sub>CH<sub>3</sub>), 2.16 (3H, s, CH<sub>3</sub>) and 1.27 (3H, t, *J* 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>).

f) **Procedure F. (Saponification) to yield 2-(5-fluoro-3-(2-(4-fluorophenylsulfonyl)benzyl)-2-methyl-1H-indol-1-yl)acetic acid**  
5  $\delta_H$  (300 MHz, *d*<sub>6</sub>-DMSO) 13.00 (1H, bs, CO<sub>2</sub>H), 8.27-8.20 (1H, m, Ar), 8.08-8.00 (2H, m, Ar), 7.60-7.45 (4H, m, Ar), 7.35 (1H, dd, *J* 8.7 and 4.3Hz, Ar), 6.99-6.93 (1H, m, Ar), 6.83 (1H, td, *J* 9.0 and 2.3Hz, Ar), 6.17 (1H, dd, *J* 9.8 and 2.6Hz, Ar), 4.98 (2H, s, NCH<sub>2</sub>), 4.18 (2H, s, ArCH<sub>2</sub>Ar) and 2.13 (3H, s, CH<sub>3</sub>). Tr = 4.60 min  
10 (95%), *m/z* (M+H)<sup>+</sup> 456.3

#### **Example 4 - Human Whole Blood Eosinophil Shape Change Assay**

Compounds 1 to 3 were assayed for their effect on PGD<sub>2</sub> induced eosinophil shape change and were compared with Comparator Compounds A to G.

15

Comparator Compound A is (5-Fluoro-2-methyl-3-quinolin-2-ylmethyl-indol-1-yl)-acetic acid.

Comparator Compound B is [5-Fluoro-3-(4-methanesulfonyl-benzyl)-2-methyl-indol-1-yl]-acetic acid.  
20

Comparator Compound C is 2-{5-Fluoro-2-methyl-3-[4-(phenylsulfonyl)benzyl]-1H-indol-1-yl}acetic acid (the 4-regioisomer of Compound 1).

25 Comparator Compound D is 2-{3-[4-(4-chlorophenylsulfonyl)benzyl]-5-fluoro-2-methyl-1H-indol-1-yl}acetic acid (the 4-regioisomer of Compound 2).

Comparator Compound E is 2-{5-Fluoro-3-[4-(4-fluorophenylsulfonyl)benzyl]-2-methyl-1H-indol-1-yl}acetic acid (the 4-regioisomer of Compound 3).

30

Comparator Compound F is 2-{5-Fluoro-2-methyl-3-[3-(phenylsulfonyl)benzyl]-1H-

indol-1-yl}acetic acid (the 3-regioisomer of Compound 1).

Comparator Compound G is 2-{3-[3-(4-chlorophenylsulfonyl)benzyl]-5-fluoro-2-methyl-1H-indol-1-yl}acetic acid (the 3-regioisomer of Compound 2).

5

### Methods

#### Shape Change Assay in whole blood

Compounds (1µl, 200 x final concentration) were added directly to 200µl whole blood, mixed well and incubated for 15 min, 37°C, 5% CO<sub>2</sub>. After this time, cell  
10 shape was fixed by addition of 300µl Cytofix™ buffer (BD Biosciences), 15 min on ice. 10ml RBC lysis buffer was added to the fixed cells, incubated 5min, at room temperature and centrifuged, 300 x g for 5 min. Supernatant (containing lysed red cells) was removed and the lysis step was repeated. Leukocytes were resuspended in 250µl RPMI/10% FCS and shape change analysed by FACS. Eosinophils were  
15 gated out based on their autofluorescence and 2000 eosinophil events were counted per sample. Data were analysed in triplicate.

### Results

The results for the eosinophil shape change assay are shown in Table 1.

20

All the compounds bound CRTH2 with a K<sub>i</sub> of less than 0.012 µM. It can be seen from Table 1 that Compounds 1 to 3 all have excellent IC<sub>50</sub> values in this assay. Comparator Compound B has comparable activity in this assay to Compounds 1 to 3 but the activity of Compound A is much lower. However, Comparator Compounds  
25 C to G, which are the para- and meta- regioisomers of Compounds 1 to 3 have comparatively poor activity in this test (of the order of 10 to 1000 times lower than that of Compounds 1 to 3).

30

**Table 1 – IC<sub>50</sub> Values for the Effect of Test Compounds on 10nm PGD<sub>2</sub>-induced Eosinophil Shape Change**

| Compound | Whole Blood IC <sub>50</sub> (μM) |       |   |
|----------|-----------------------------------|-------|---|
|          | Value                             | SEM   | n |
| 1        | 0.005                             | 0.003 | 3 |
| 2        | 0.002                             | 0.001 | 3 |
| 3        | 0.006                             | 0.003 | 3 |
| A        | 0.103                             | 0.009 | 4 |
| B        | 0.008                             | 0.002 | 3 |
| C        | 0.273                             | 0.175 | 3 |
| D        | 0.494                             | NA    | 1 |
| E        | 0.071                             | 0.008 | 2 |
| F        | 1.50                              | N/A   | 1 |
| G        | 4.66                              | N/A   | 1 |

5

**Example 5 – Investigation of Pharmacokinetics of Compounds of General Formula (I) Following Oral Administration in the Rat**

**Experimental procedures**

10    **a)    Weighing of rats**

Rats were weighed on the day of dosing.

**b)    Dose preparation**

15    The test material was prepared as a 0.3mg/mL suspension in 1% carboxy-methyl-cellulose (CMC).

**c)    Dose regimen**

Three groups of 3 rats were dosed as follows:

| Group No. | Treatment  | Dose (mg/kg) | Route |
|-----------|------------|--------------|-------|
| 20    1   | Compound 1 | 3            | oral  |
| 2         | Compound 2 | 3            | oral  |
| 3         | Compound 3 | 3            | oral  |

**d) Dose administration**

Doses were administered as a single oral dose using a gavage tube at a constant dose volume of 10 mL/kg.

**5 e) Blood sample collection**

At each sampling time point blood samples (approximately 0.3 mL) was taken from a catheter inserted into a lateral tail vein prior to the start of the experiment. The final blood sample (approximately 2mL) from each animal was taken by cardiac puncture under isoflurane anaesthesia following which the animal was killed by  
10 exsanguination. Blood samples were taken into individual heparinised containers. Blood samples were collected at the following times post-dose:  
15, 30, 60, 120, 240, 360, 480, 720 minutes and 24 hours

Following collection, the blood samples were centrifuged (approximately 10,000 x g,  
15 2 min at 4°C) and the plasma stored as one aliquot at approximately -20°C pending analysis of drug concentrations by LC-MS/MS.

**f) Sample Bioanalysis**

The plasma samples were analysed for test material concentrations at BioDynamics  
20 using an LC-MS/MS method developed at BioDynamics.

**Results**

The pharmacokinetic profile of a compound is important as it illustrates how much of a compound will remain in the body for how long and the exposure of a subject to a  
25 compound when administered orally.

The results for the blood concentrations of Compounds 1, 2, 3, A and B are shown in Tables 2, 3, 4, 5 and 6 respectively.

30 A compound which is intended to be administered orally, will ideally need to be taken only once or twice daily as this reduces the burden on the patient and thus increases patient compliance. Therefore, it is greatly preferred that after 12 hours,

the concentration of drug remaining in the blood is as at least as great as the  $IC_{50}$  value for the compound and preferably considerably higher than this. An even more favourable pharmacokinetic profile is one in which the concentration remaining in the blood after 24 hours is at least as great as the  $IC_{50}$  value for the compound and preferably considerably higher than this.

**Table 2 – Concentration of Compound 1 in blood (ng/mL) after oral administration to rats at a dose of 3mg/kg**

| Concentration in Blood (ng/mL) |        |        |        |        |       |
|--------------------------------|--------|--------|--------|--------|-------|
| Time (h)                       | Male 4 | Male 5 | Male 6 | Mean   | SD    |
| 0.25                           | 1161.2 | 1496.0 | 1678.0 | 1445.1 | 262.1 |
| 0.5                            | 2681.3 | 2792.4 | 3264.7 | 2912.8 | 309.8 |
| 1                              | 3835.5 | 3895.3 | 4262.9 | 3997.9 | 231.4 |
| 2                              | 4330.9 | 3454.7 | 4051.1 | 3945.6 | 447.5 |
| 4                              | 1890.9 | 1046.5 | 1670.8 | 1536.1 | 438.0 |
| 6                              | 1423.7 | 547.5  | 1183.1 | 1051.4 | 452.7 |
| 8                              | 1099.9 | 404.7  | 696.2  | 733.6  | 349.1 |
| 12                             | 455.4  | 256.6  | 412.8  | 374.9  | 104.7 |
| 24                             | 68.5   | 10.2   | 63.5   | 47.4   | 32.3  |

The results in Table 2 show that after 24 hours, the mean amount of Compound 1 remaining in the blood was 47.4ng/mL. The  $IC_{50}$  of Compound 1 in the whole blood eosinophil shape change assay is 5 nM (2.2 ng/ml) and is therefore *ca.* 21 times over the whole blood eosinophil shape change  $IC_{50}$  at 24hrs. The results therefore show that Compound 1 is particularly suitable for oral administration to a patient.

**Table 3 - Concentration of Compound 2 in blood (ng/mL) after oral administration to rats at a dose of 3mg/kg**

| Time (h) | Male 7 | Male 8 | Male 9 | Mean   | SD    |
|----------|--------|--------|--------|--------|-------|
| 0.25     | 1569.4 | 1297.7 | 1608.1 | 1491.7 | 169.1 |
| 0.5      | 2612.1 | 1770.2 | 2276.6 | 2219.6 | 423.8 |
| 1        | 2958.2 | 2367.1 | 3366.1 | 2897.1 | 502.3 |
| 2        | 2239.9 | 2536.9 | 2717.6 | 2498.1 | 241.2 |
| 4        | 1128.4 | 1319.1 | 1666.5 | 1371.3 | 272.8 |
| 6        | 519.6  | 368.3  | 1032.6 | 640.2  | 348.2 |
| 8        | 423.7  | 186.7  | 740.4  | 450.3  | 277.8 |
| 12       | 144.7  | 28.2   | 128.1  | 100.3  | 63.0  |
| 24       | 60.5   | 0.0    | 0.0    | ND     | 0.0   |

The results in Table 3 show that after 12 hours, the mean amount of Compound 2 remaining in the blood was 100.3 ng/mL. The results at 24 hours were less consistent and the mean was not determined at this time. The IC<sub>50</sub> of Compound 2 in the whole blood eosinophil shape change assay is 2 nM (0.9 ng/ml) and is therefore *ca.* 111 times over the whole blood eosinophil shape change IC<sub>50</sub> at 12hrs. The results therefore show that Compound 2 is suitable for oral administration to a patient, although the profile is not as favourable as that of Compound 1.

**10 Table 4 - Concentration of Compound 3 in blood (ng/mL) after oral administration to rats at a dose of 3mg/kg**

| Time (h) | Male 13 | Male 14 | Male 15 | Mean   | SD    |
|----------|---------|---------|---------|--------|-------|
| 0.25     | 835.8   | 1130.7  | 1337.2  | 1101.2 | 252.0 |
| 0.5      | 2056.6  | 2205.2  | 2487.5  | 2249.8 | 218.9 |
| 1        | 2487.6  | 3547.8  | 3393.7  | 3143.0 | 572.8 |
| 2        | 4320.6  | 3685.1  | 4221.0  | 4075.6 | 341.8 |
| 4        | 3132.0  | 2023.1  | 2053.8  | 2403.0 | 631.5 |
| 6        | 1333.7  | 995.0   | 1098.0  | 1142.2 | 173.6 |
| 8        | 1163.7  | 699.5   | 678.5   | 847.2  | 274.3 |
| 12       | 465.3   | 163.3   | 201.1   | 276.6  | 164.5 |
| 24       | 38.2    | 0.0     | 10.1    | 16.1   | 19.8  |

The results in Table 4 show that after 24 hours, the mean amount of Compound 3 remaining in the blood was 16.1 ng/mL. The IC<sub>50</sub> of Compound 1 in the whole blood eosinophil shape change assay is 6 nM (2.7 ng/ml) and is therefore *ca.* 6 times over the whole blood eosinophil shape change IC<sub>50</sub> at 24hrs. The results therefore show that Compound 3 is particularly suitable for oral administration to a patient.

20 The results in Table 5 show that after 24 hours, the mean amount of Compound (A) remaining in the blood was 43.7 ng/mL. The IC<sub>50</sub> of Compound 1 in the whole blood eosinophil shape change assay is 103 nM (35.8 ng/ml) and is therefore *ca.* 1.2 times over the whole blood eosinophil shape change IC<sub>50</sub> at 24hrs.

**Table 5 - Concentration of Compound (A) in blood (ng/mL) after oral administration to rats at a dose of 3mg/kg**

| Time (h) | Male 4 | Male 5 | Male 6 | Mean   | Stdev |
|----------|--------|--------|--------|--------|-------|
| 0.25     | 139.1  | 153.9  | 68.3   | 120.4  | 45.8  |
| 0.5      | 425.6  | 388.4  | 256.3  | 356.8  | 89.0  |
| 1        | 875.2  | 923.2  | 538.8  | 779.1  | 209.5 |
| 2        | 1415.1 | 1309.0 | 1013.6 | 1245.9 | 208.1 |
| 4        | 923.1  | 820.5  | 827.0  | 856.9  | 57.5  |
| 6        | 404.3  | 514.8  | 432.6  | 450.6  | 57.4  |
| 8        | 305.6  | 521.9  | 235.5  | 354.3  | 149.3 |
| 24       | 51.8   | 79.2   | 0.0    | 43.7   | 40.2  |

**5 Table 6 - Concentration of Compound (B) in blood (ng/mL) after oral administration to rats at a dose of 3mg/kg**

| Time (h) | Male 31 | Male 32 | Male 33 | Mean  | Stdev |
|----------|---------|---------|---------|-------|-------|
| 0.25     | 91.8    | 113.6   | 57.3    | 87.6  | 28.4  |
| 0.5      | 121.2   | 165.7   | 132.1   | 139.7 | 23.2  |
| 1        | 252.1   | 295.1   | 217.5   | 254.9 | 38.9  |
| 2        | 349.9   | 536.9   | 256.2   | 381.0 | 142.9 |
| 4        | 179.4   | 485.2   | 184.9   | 283.2 | 175.0 |
| 6        | 128.3   | 292.2   | 125.8   | 182.1 | 95.4  |
| 8        | 72.1    | 184.5   | 84.7    | 113.8 | 61.6  |
| 12       | 36.5    | 31.0    | 14.5    | 27.3  | 11.4  |
| 24       | 0       | 0       | 0       | 0     | 0     |

The results in Table 6 show that after 12 hours, the mean amount of Compound B remaining in the blood was 27.3 ng/mL. The  $IC_{50}$  of Compound B in the whole blood eosinophil shape change assay is 8 nM (3.0 ng/ml) and is therefore ca. 9.1 times over the whole blood eosinophil shape change  $IC_{50}$  at 12hrs.

Figures 1 to 5 are plots blood concentration of compound versus time for rats dosed orally with 3mg/kg of Compounds 1, 2, 3, A and B respectively. They are therefore graphical representations of the data set out in Tables 2 to 6.

The values for  $C_{max}$  (maximum blood concentration),  $T_{max}$  (time at which  $C_{max}$  occurs),  $AUC_{inf}$  (area under curve to infinity) and  $T_{1/2}$  (half life) taken from Figures 1 to 5 are set out in Tables 7 to 11 for Compounds 1, 2, 3, A and B respectively.

The values for  $C_{\max}$  and the  $AUC_{\text{inf}}$  represent the exposure of a subject to an oral dose of the compound. It is therefore preferred that the figures for both  $C_{\max}$  and AUC should be as high as possible so that exposure to the compound is maximised.

5

**Table 7 - PK Parameters for 3 mg/kg Compound 1 p.o**

| Parameter          | Units     | Male 4 | Male 5 | Male 6 | Mean  |
|--------------------|-----------|--------|--------|--------|-------|
| C <sub>max</sub>   | ng/mL     | 4331   | 3895   | 4263   | 4163  |
| T <sub>max</sub>   | hours     | 2      | 1      | 1      | 1.3   |
| AUC <sub>inf</sub> | ng/mL*hrs | 23809  | 14846  | 21731  | 19328 |
| T <sub>1/2</sub>   | hours     | 4.11   | 3.07   | 4.59   | 3.6   |

**Table 8 - PK Parameters for 3 mg/kg Compound 2 p.o**

| Parameter          | Units     | Male 7 | Male 8 | Male 9 | Mean  |
|--------------------|-----------|--------|--------|--------|-------|
| C <sub>max</sub>   | ng/mL     | 2958.0 | 2537.0 | 3366.0 | 2954  |
| T <sub>max</sub>   | hours     | 1.0    | 2.0    | 1.0    | 1.3   |
| AUC <sub>inf</sub> | ng/mL*hrs | 13153  | 10179  | 15677  | 11666 |
| T <sub>1/2</sub>   | hours     | 6      | 2      | 2      | 3.7   |

10

**Table 9 - PK Parameters for 3 mg/kg Compound 3 p.o**

| Parameter          | Units     | Male 13 | Male 14 | Male 15 | Mean  |
|--------------------|-----------|---------|---------|---------|-------|
| C <sub>max</sub>   | ng/mL     | 4321    | 3685    | 4221    | 4076  |
| T <sub>max</sub>   | hours     | 2       | 2       | 2       | 2.0   |
| AUC <sub>inf</sub> | ng/mL*hrs | 24379   | 17738   | 19110   | 21059 |
| T <sub>1/2</sub>   | hours     | 3.26    | 2.26    | 2.62    | 2.8   |

15

**Table 10 - PK Parameters for 3 mg/kg Compound (A) p.o**

| Parameter          | Units     | Male 4 | Male 5  | Male 6 | Mean   |
|--------------------|-----------|--------|---------|--------|--------|
| C <sub>max</sub>   | ng/mL     | 1415.1 | 1309.0  | 1013.6 | 1245.9 |
| T <sub>max</sub>   | hours     | 2.0    | 2.0     | 2.0    | 2.0    |
| AUC <sub>inf</sub> | ng/mL*hrs | 8570.4 | 10429.2 | 5473.9 | 8157.8 |
| T <sub>1/2</sub>   | hours     | 6.1    | 6.1     | 2.2    | 4.8    |

**Table 11 - PK Parameters for 3 mg/kg Compound (B) p.o**

| Parameter          | Units     | Male 4 | Male 5 | Male 6 | Mean   |
|--------------------|-----------|--------|--------|--------|--------|
| C <sub>max</sub>   | ng/mL     | 349.9  | 536.9  | 256.2  | 381.0  |
| T <sub>max</sub>   | hours     | 2.0    | 2.0    | 2.0    | 2.0    |
| AUC <sub>inf</sub> | ng/mL*hrs | 1831.4 | 3256.1 | 1505.1 | 2197.6 |
| T <sub>1/2</sub>   | hours     | 3.41   | 1.80   | 1.86   | 2.4    |

- 5 From Tables 7 to 11 it can be seen that Compounds 1, 2 and 3 have mean C<sub>max</sub> values of 4163, 2954 and 4076 respectively. In contrast, the mean values for Compounds A and B are only 1245.9 and 381.0.

- The AUC<sub>inf</sub> values for Compounds 1, 2 and 3 are 19238, 11666 and 21059, while  
10 those for Compounds A and B are 8157.8 and 2197.6.

- Thus the figures for both C<sub>max</sub> and AUC<sub>inf</sub> are significantly higher for the compounds of the present invention than those for Comparator Compounds A and B. It is clear from these results that subjects dosed orally with Compounds A and B would have  
15 much lower exposure to the drug than subjects dosed orally with Compounds 1, 2 and 3.

- The results from Examples 4 and 5 are summarised in Table 12, in which the Fold over IC<sub>50</sub> at 12 h is defined as the mean amount of compound remaining in the blood  
20 at 12 hours in ng/ml divided by the IC<sub>50</sub> of the compound in ng/ml. Similarly the fold over IC<sub>50</sub> at 24 h is defined as is defined as the mean amount of compound remaining in the blood at 24 hours in ng/ml divided by the IC<sub>50</sub> of the compound in ng/ml.

**Table 12**

| <b>Compound</b>                          | <b>1</b> | <b>2</b> | <b>3</b> | <b>A</b> | <b>B</b> |
|------------------------------------------|----------|----------|----------|----------|----------|
| <b>IC<sub>50</sub> (μmol)</b>            | 0.005    | 0.002    | 0.006    | 0.103    | 0.008    |
| <b>IC<sub>50</sub> (ng/mL)</b>           | 2.2      | 0.9      | 2.7      | 35.8     | 3.0      |
| <b>Fold over IC<sub>50</sub> at 12 h</b> | 170      | 111      | 102      | ND       | 9.1      |
| <b>Fold over IC<sub>50</sub> at 24 h</b> | 21       | ND       | 6        | 1.2      | 0        |
| <b>C<sub>max</sub></b>                   | 4163     | 2954     | 4076     | 1246     | 381      |
| <b>AUC<sub>inf</sub></b>                 | 19328    | 11666    | 21059    | 8158     | 2198     |

- Table 12 shows that Comparator Compound A has a higher IC<sub>50</sub> than Compounds 1, 2 and 3 and a lower value for fold over IC<sub>50</sub> at 24 hours than Compounds 1 and 3.
- 5 The exposure of a subject to the drug after oral administration as indicated by C<sub>max</sub> and AUC<sub>inf</sub> is significantly lower for Compound A than for any of Compounds 1 to 3.

- Compound B has an IC<sub>50</sub> value which is comparable to that of Compounds 1, 2 and
- 10 3. However, the fold over IC<sub>50</sub> at 12 and 24 hours is significantly less favourable than that of any of Compounds 1 to 3 and the exposure of a subject to the drug after oral administration as indicated by C<sub>max</sub> and AUC<sub>inf</sub> is significantly lower for Compound B than for any of Compounds 1 to 3.

- 15 Comparator Compounds A and B each have some properties which are comparable with those of Compounds 1, 2 and 3. However, taken as a whole, their properties are less favourable than those of the compounds of the invention.

- 20 **Example 6 – Evaluation of Compounds of General Formula (I) as Inhibitors of 13,14-dihydro-15-keto prostaglandin D2 (DK-PGD2)– induced blood eosinophilia in rats**

### **Protocol**

- 25 The test compound was dissolved in DMSO and diluted with water to give a final dosing volume of 2 ml/kg.

Female rats (175 – 250g; UH colony) were dosed orally with test compound (or vehicle).

30 min after dosing all animals were anaesthetised with isoflurane.

Following induction of anaesthesia, animals receive an intracardiac injection of 10µg  
5 DK-PGD<sub>2</sub> in 0.3ml heparinised (10U/ml) saline. Control animals received an  
injection of 0.3ml heparinised saline.

60 min after the intracardiac injection, animals were injected with an overdose of  
pentobarbitone sodium and a blood sample was taken (into heparin) by cardiac  
10 puncture while the rat was anaesthetised but not dead.

An aliquot of blood (100 µl) was added to Turk's solution and the total leukocyte  
count determined with a haemocytometer.

15 A further aliquot of blood (500µl) was mixed with an equal volume of 4% Dextran  
(mw 500,000) and the erythrocytes allowed to settle. A cytopsin preparation was  
made from the resulting leukocyte rich fraction.

Cytospin preparations were fixed with methanol (5 min) and stained with May-  
20 Grunwald (5min) and Giemsa (15 min) stains. Finally cytopsin were washed in  
phosphate buffer (pH6.8) and air dried.

Differential leukocyte counts were obtained from the cytopsin preparations.

25 Blood eosinophil numbers were determined from the total leukocyte count and the  
percentage eosinophils (differential count).

### **Experimental design**

Up to 12 animals were used in each experiment. Groups included:

30 Untreated controls

DK-PGD<sub>2</sub>-induced eosinophilia, vehicle treated animals (positive control)

DK-PGD<sub>2</sub>-induced eosinophilia, Compound 1; doses of 0.0001, 0.001, 0.01 and 0.1 µg/kg p.o.

DK-PGD<sub>2</sub>-induced eosinophilia, Compound 2; doses of 0.001, 0.01, 0.1 and 1.0 µg/kg p.o.

5 DK-PGD<sub>2</sub>-induced eosinophilia , Compound 3; doses of 0.001, 0.01, 0.1 and 1.0 µg/kg p.o.

DK-PGD<sub>2</sub>-induced eosinophilia , Compound A; doses of 0.01, 0.1 and 1.0 mg/kg p.o.

DK-PGD<sub>2</sub>-induced eosinophilia , Compound A; doses of 0.001, 0.01, 0.1 and 1.0 mg/kg p.o.

10

Because it was impractical to generate sufficient data in any given experiment, data were obtained over a number of replicate experiments. Data from these replicate experiments were pooled, to provide at least 5 animals in each group and a dose-response curve fitted following a significance test (Mann Whitney) to determine whether or not DK-PGD<sub>2</sub> caused a significant increase in blood eosinophils(GraphPad, Prism). A difference between groups was taken to be significant when P<0.05. ED50 values were calculated from the dose-response curve.

15

20 The results of these experiments are shown in Figures 6 to 10 and in Table 13 below.

**Table 13**

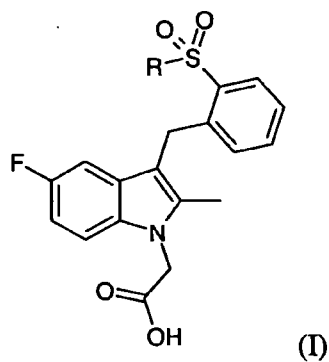
| Compound                                                                         | 1      | 2     | 3     | A  | B  |
|----------------------------------------------------------------------------------|--------|-------|-------|----|----|
| Potency in inhibition of DK-PGD <sub>2</sub> -induced blood eosinophilia (µg/ml) | 0.0025 | 0.010 | 0.010 | 37 | 17 |

It can be seen from Table 13 and Figures 6-10 that Compounds 1-3 are several thousand times more potent than Comparator Compounds A and B in inhibiting DK-PGD<sub>2</sub>-induced blood eosinophilia in rats.

25

CLAIMS

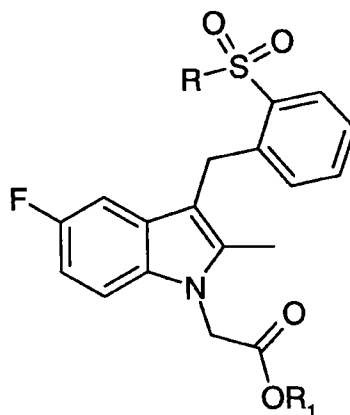
1. A compound of general formula (I)



5

wherein R is phenyl optionally substituted with one or more halo substituents;  
or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof.

2. A compound of general formula (II):



II

15

wherein R is as defined for general formula (I); and

$R^1$  is  $C_1$ - $C_6$  alkyl, aryl,  $(CH_2)_mOC(=O)C_1$ - $C_6$ alkyl,  $(CH_2)_mN(R^{11})_2$ ,



m is 1 or 2;

$\text{R}^{11}$  is hydrogen or methyl;

$\text{R}^{12}$  is  $\text{C}_1$ - $\text{C}_{18}$  alkyl.

5

3. A compound as claimed in claim 1 or claim 2, wherein the phenyl group R is unsubstituted or is substituted with a single halo substituent.

4. A compound as claimed in claim 3, wherein the halo substituent is fluoro or  
10 chloro

5. A compound as claimed in claim 4, wherein the fluoro or chloro substituent is at the 4-position of the phenyl group R.

15 6. A compound as claimed in claim 1 or claim 2 which is:

2-{5-Fluoro-2-methyl-3-[2-(phenylsulfonyl)benzyl]-1H-indol-1-yl}acetic acid;

2-{3-[2-(4-chlorophenylsulfonyl)benzyl]-5-fluoro-2-methyl-1H-indol-1-yl}acetic acid;

20 2-{5-Fluoro-3-[2-(4-fluorophenylsulfonyl)benzyl]-2-methyl-1H-indol-1-yl}acetic acid;

or the  $\text{C}_1$ - $\text{C}_6$  alkyl, aryl,  $(\text{CH}_2)_m\text{OC}(=\text{O})\text{C}_1$ - $\text{C}_6$ alkyl,  $(\text{CH}_2)_m\text{N}(\text{R}^{11})_2$ ,

$\text{CH}((\text{CH}_2)_m\text{O}(\text{C}=\text{O})\text{R}^{12})_2$  esters of any of the above; wherein

m is 1 or 2;

$\text{R}^{11}$  is hydrogen or methyl;

25  $\text{R}^{12}$  is  $\text{C}_1$ - $\text{C}_{18}$  alkyl.

7. A process for the preparation of a compound of general formula (I) as claimed in any one of claims 1 to 6, the process comprising reacting a compound of general formula (II) as defined in claim 2 and wherein  $\text{R}^1$  is  $\text{C}_1$ - $\text{C}_6$  alkyl with a base.

30

8. A compound as claimed in any one of claims 1 to 6 for use in medicine.

9. A compound as claimed in any one of claims 1 to 6 for use in the treatment of asthma, including allergic asthma, bronchial asthma, exacerbations of asthma and related allergic diseases caused by viral infection, particularly those exacerbations  
5 caused by rhinovirus and respiratory syncytial virus intrinsic, extrinsic, exercise-induced, drug-induced and dust-induced asthma, treatment of cough, including chronic cough associated with inflammatory and secretory conditions of the airways and iatrogenic cough, acute and chronic rhinitis, including rhinitis medicamentosa, vasomotor rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis, nasal  
10 polyposis, acute viral infection including common cold, infection due to respiratory syncytial virus, influenza, coronavirus and adenovirus, atopic dermatitis, contact hypersensitivity (including contact dermatitis), eczematous dermatitis, phyto dermatitis, photo dermatitis, sebhorroic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosis et atrophica, pyoderma gangrenosum, skin sarcoid, discoid  
15 lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme, cellulitis, panniculitis, cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; blepharitis conjunctivitis, especially allergic  
20 conjunctivitis, anterior and posterior uveitis, choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis; bronchitis, including infectious and eosinophilic bronchitis, emphysema, bronchiectasis, farmer's lung, hypersensitivity pneumonitis, idiopathic interstitial pneumonias, complications of lung transplantation, vasculitic and thrombotic disorders of the lung vasculature,  
25 pulmonary hypertension, food allergies, gingivitis, glossitis, periodontitis, oesophagitis including reflux, eosinophilic gastroenteritis, proctitis, pruritis ani, celiac disease, food-related allergies, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other CRTH2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura,  
30 eosinophilic paschiitis, antiphospholipid syndrome and systemic lupus

erythematosus, AIDS, leprosy, Sezary syndrome, paraneoplastic syndrome, mixed and undifferentiated connective tissue diseases, inflammatory myopathies including dermatomyositis and polymyositis, polymyalgia rheumatica, juvenile arthritis, rheumatic fever, vasculitides including giant cell arteritis, Takayasu's arteritis, 5 Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, temporal arteritis, myasthenia gravis, acute and chronic pain, neuropathic pain syndromes, neurodegeneration, central and peripheral nervous system complications of malignant, infectious or autoimmune processes, low back pain, familial Mediterranean Fever, Muckle-Wells syndrome, Familial Hibernian fever, Kikuchi 10 disease, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, Still's disease, ankylosing spondylitis, reactive arthritis, undifferentiated spondyloarthritis, psoriatic arthritis, septic arthritis and other infection-related arthropathies and bone disorders and osteoarthritis; acute and chronic crystal-induced synovitis including urate gout, 15 calcium pyrophosphate deposition disease, calcium phosphate related tendon syndrome and synovial inflammation, Behcet's disease, primary and secondary Sjogren's syndrome systemic sclerosis and limited scleroderma; hepatitis, cirrhosis of the liver, cholecystitis, pancreatitis, nephritis, nephritic syndrome, cystitis and Hunner's ulcer, acute and chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvo- 20 vaginitis, Peyronie's disease, erectile dysfunction, Alzheimer's disease and other dementing disorders; pericarditis, myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid, ischaemic reperfusion injuries, endocarditis, valvulitis, aortitis, phlebitis, thrombosis, treatment of common cancers and fibrotic conditions such as idiopathic pulmonary fibrosis including cryptogenic 25 fibrosing alveolitis, keloids, excessive fibrotic scarring/adhesions post surgery, liver fibrosis including that associated with hepatitis B and C, uterine fibroids, sarcoidosis, including neurosarcoidosis, scleroderma, kidney fibrosis resulting from diabetes, fibrosis associated with RA, atherosclerosis, including cerebral atherosclerosis, vasculitis, myocardial fibrosis resulting from myocardial infarction, cystic fibrosis, 30 restenosis, systemic sclerosis, Dupuytren's disease, fibrosis complicating anti-neoplastic therapy and chronic infection including tuberculosis and aspergillosis and

other fungal infections, CNS fibrosis following stroke or the promotion of healing without fibrotic scarring.

10. The use of a compound as claimed in any one of claims 1 to 6 in the  
5 preparation of an agent for the treatment or prevention of asthma, including allergic asthma, bronchial asthma, exacerbations of asthma and related allergic diseases caused by viral infection, particularly those exacerbations caused by rhinovirus and respiratory syncytial virus intrinsic, extrinsic, exercise-induced, drug-induced and dust-induced asthma, treatment of cough, including chronic cough associated with  
10 inflammatory and secretory conditions of the airways and iatrogenic cough, acute and chronic rhinitis, including rhinitis medicamentosa, vasomotor rhinitis, perennial allergic rhinitis, seasonal allergic rhinitis, nasal polyposis, acute viral infection including common cold, infection due to respiratory syncytial virus, influenza, coronavirus and adenovirus, atopic dermatitis, contact hypersensitivity (including  
15 contact dermatitis), eczematous dermatitis, phyto dermatitis, photo dermatitis, sebhorroic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosis et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness,  
20 Sweet's syndrome, Weber-Christian syndrome, erythema multiforme, cellulitis, panniculitis, cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; blepharitis conjunctivitis, especially allergic conjunctivitis, anterior and posterior uveitis, choroiditis, autoimmune, degenerative or inflammatory disorders affecting the retina, ophthalmitis; bronchitis, including infectious and eosinophilic  
25 bronchitis, emphysema, bronchiectasis, farmer's lung, hypersensitivity pneumonitis, idiopathic interstitial pneumonias, complications of lung transplantation, vasculitic and thrombotic disorders of the lung vasculature, pulmonary hypertension, food allergies, gingivitis, glossitis, periodontitis, oesophagitis including reflux, eosinophilic gastroenteritis, proctitis, pruritis ani, celiac disease, food-related allergies,  
30 inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other CRTH2-mediated diseases, for example autoimmune diseases such as

hyper IgE syndrome, Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic paschiitis, antiphospholipid syndrome and systemic lupus erythematosus, AIDS, leprosy, Sezary syndrome, paraneoplastic syndrome, mixed and undifferentiated connective  
5 tissue diseases, inflammatory myopathies including dermatomyositis and polymyositis, polymyalgia rheumatica, juvenile arthritis, rheumatic fever, vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, temporal arteritis, myasthenia gravic, acute and chronic pain, neuropathic pain syndromes, central and peripheral nervous  
10 system complications of malignant, infectious or autoimmune processes, low back pain, familial Mediterranean Fever, Muckle-Wells syndrome, Familial Hibernian fever, Kikuchi disease, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury, chronic obstructive pulmonary disease, as well as rheumatoid arthritis, Still's disease, ankylosing spondylitis, reactive arthritis, undifferentiated  
15 spondarthropathy, psoriatic arthritis, septic arthritis and other infection-related arthropathies and bone disorders and osteoarthritis; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, calcium paptite related tendon syndrome and synovial inflammation, Behcet's disease, primary and secondary Sjogren's syndrome systemic sclerosis and limited  
20 scleroderma; hepatitis, cirrhosis of the liver, cholecystitis, pancreatitis, nephritis, nephritic syndrome, cystitis and Hunner's ulcer, acute and chronic urethritis, prostatitis, epididymitis, oophoritis, salpingitis, vulvo-vaginitis, Peyronie's disease, erectile dysfunction, Alzheimer's disease and other dementing disorders; pericarditis, myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial  
25 sarcoid, ischaemic reperfusion injuries, endocarditis, valvulitis, aortitis, phlebitis, thrombosis, treatment of common cancers and fibrotic conditions such as idiopathic pulmonary fibrosis including cryptogenic fibrosing alveolitis, keloids, excessive fibrotic scarring/adhesions post surgery, liver fibrosis including that associated with hepatitis B and C, uterine fibroids, sarcoidosis, including neurosarcoidosis,  
30 scleroderma, kidney fibrosis resulting from diabetes, fibrosis associated with RA, atherosclerosis, including cerebral atherosclerosis, vasculitis, myocardial fibrosis

resulting from myocardial infarction, cystic fibrosis, restenosis, systemic sclerosis, Dupuytren's disease, fibrosis complicating anti-neoplastic therapy and chronic infection including tuberculosis and aspergillosis and other fungal infections, CNS fibrosis following stroke or the promotion of healing without fibrotic scarring.

5

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 6 together with a pharmaceutical excipient or carrier.

12. A composition as claimed in claim 11 formulated for oral, rectal, nasal,  
10 bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration.

13. A composition as claimed in claim 11 or claim 12 containing one or more  
15 additional active agents useful in the treatment of diseases and conditions mediated by PGD<sub>2</sub> or other agonists at the CRTH2 receptor.

14. A composition as claimed in claim 13, wherein the additional active agents are selected from:

20 other CRTH2 antagonists;

Suplatast tosylate and similar compounds;

$\beta_1$  to  $\beta_4$  adrenoreceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate and pirbuterol or methylxanthanines such as theophylline and

25 aminophylline, mast cell stabilisers such as sodium cromoglycate or muscarinic receptor (M1, M2 or M4) antagonists;

antihistamines, for example histamine H<sub>1</sub> receptor antagonists such as loratidine cetirizine, desloratidine, fexofenadine, astemizole, azelastine and chlorpheniramine or histamine H<sub>2</sub> or H<sub>4</sub> receptor antagonists;

30  $\alpha_1$  and  $\alpha_2$  adrenoreceptor agonists such as propylhexedrine phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline

- hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride and ethylnorepinephrine hydrochloride;
- insulin-like growth factor (IGF-1) mimetics;
- matrix metalloprotease (MMP) inhibitors, for example inhibitors of stromelysins,
- 5 collagenases gelatinases and aggrecanase, especially collagenase-1, collagenase-2, collagenase-3, stromelysin-1, stromelysin-2, stromelysin-3 and MMP-12;
- modulators of chemokine receptor function, for example CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family) or CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-
- 10 X-C family) and CX<sub>3</sub>CR1 for the C-X<sub>3</sub>-C family;
- antiviral agents such as Viracept, AZT, acyclovir and famciclovir and antiseptics compounds such as Valant;
- cardiovascular agents, for example calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, ACE inhibitors, Angiotensin-2 receptor
- 15 antagonists and platelet aggregation inhibitors;
- CNS agents, for example antidepressants such as sertraline, anti-Parkinsonian drugs such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, COMT inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine antagonists, Dopamine agonists and
- 20 inhibitors of neuronal nitric oxide synthase and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metyfonate;
- Tryptase inhibitors;
- Platelet activating factor (PAF) antagonists;
- Interleukin converting enzyme (ICE) inhibitors;
- 25 IMPDH inhibitors;
- Adhesion molecule inhibitors including VLA-4 antagonists;
- Cathepsins;
- MAP kinase inhibitors;
- Glucose-6-phosphonate dehydrogenase inhibitors;
- 30 Kinin-B<sub>1</sub> and B<sub>2</sub> receptor antagonists;
- Anti-gout agents such as colchicine;

- Xantine oxidase inhibitors such as allopurinol;  
Uricosuric agents, such as probenecid, dulfipyrasone and benzbromarone;  
Growth hormone secretagogues;  
Transforming growth factor beta (TGF $\beta$ );  
5 Platelet-derived growth factor (PDGF)  
Fibroblast growth factor e.g. basic fibroblast growth factor  
Granulocyte macrophage colony stimulating factor (GM-CSF);  
Capsaicin;  
Tachykinin NK<sub>1</sub> and NK<sub>3</sub> receptor antagonists such as NKP-608C, talnetant and D-  
10 4418;  
Elastase inhibitors such as UT-77 and ZD-0892;  
Induced nitric oxide synthase inhibitors (iNOS);  
Osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax;  
anticholinergic agents such as ipratropium bromide, tiotropium bromide, oxitropium  
15 bromide, pirenzepine and telenzepine;  
leukotriene antagonists (LTB<sub>4</sub>, LTD<sub>4</sub> and LTE<sub>4</sub> antagonists) such as phenothiazine-3-  
ones such as L-651,392, amidino compounds such as CGS-25019c, benzoxalamines  
such as ontazolast, benzene carboximidamides such as BIII 284/260 and compounds  
such as zafirlukast, ablukast, montelukast, pranlukast, verlukast, RG-12525, Ro-  
20 245913, iralukast and BAY x 7195;  
leukotriene biosynthesis inhibitors such as 5-lipoxygenase inhibitors or 5-  
lipoxygenase activating protein (FLAP) inhibitors such as zileuton, ABT-761,  
fenleuton, tepoxalin, Abbott-79175, N-(5-substituted)-thiophene-2-  
alkylsulfonamides, 2,6-di-tert-butylphenol hydrazones, methoxytetrahydropyrans  
25 such as ZD2138, SB-210661, pyridinyl-substituted-2-cyanonaphthalene compounds  
such as L-739010, 2-cyanoquinoline compounds such as L-746,530, indole and  
quinoline compounds such as MK-591, MK-886 and BAY x 1005;  
Phosphodiesterase inhibitors, including PDE4 inhibitors such as PDE4D inhibitors;  
anti-IgE antibody therapies such as omalizumab;  
30 anti-infectives such as fusidic acid (particularly for the treatment of atopic  
dermatitis);

- anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis); immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease or alternatively FK-506, rapamycin, cyclosporine, azathioprine or methotrexate;
- 5 antiproliferative/antineoplastic drugs such as alkylating agents, e.g. cisplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas, antimetabolites, e.g. antifolates such as fluoropyrimidines such as 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel;
- 10 antitumour antibiotics such as anthracyclines such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and methramycin;
- antimitotic agents such as vinca alkaloids including vincristine, vinblastine, vindesine and vinorelbine and taxoides such as taxol and taxostere and
- 15 topoisomerase inhibitors such as epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin; cytostatic agents such as antioestrogens such as tamoxifen, toremifene, raloxifene, droloxifene and idoxifene, oestrogen receptor down regulators such as fulvestrant, antiandrogens such as bicalutamide, flutamide, nilutamide and cyproterone acetate, LHRH antagonists or agonists such as goserelin,
- 20 leuprorelin and buserelin, progestogens such as megestrol acetate, aromatase inhibitors such as anastrozole, letrozole, boraazole and exemestane and inhibitors of 5 $\alpha$  reductase such as finasteride;
- agents which inhibit cancer cell invasion, for example metalloproteinase inhibitors such as marimastat and inhibitors of urokinase plasminogen activator receptor
- 25 function;
- inhibitors of growth factor function for example growth factor antibodies, growth factor receptor antibodies, e.g. the anti-erbB2 antibody trastuzumab and the anti-erbB1 antibody cetuximab, farnesyl transferase inhibitors, tyrosine kinase inhibitors and serine or threonine kinase inhibitors, for example inhibitors of the epidermal
- 30 growth factor family such as EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine

- (gefitinib), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033), or inhibitors of the platelet derived growth factor or the hepatocyte growth factor families;
- 5 antiangiogenic agents, particularly those which inhibit the effects of vascular endothelial growth factor e.g. the anti-vascular endothelial cell growth factor antibody bevacizumab and also compounds that work by other mechanisms e.g. linomide, inhibitors of integrin  $\alpha v \beta 3$  function and angiostatin; vascular damaging agents such as Combretastatin A4;
- 10 antisense therapies such as those which are directed to targets listed above, e.g. ISIS 2503, an anti-ras antisense; gene therapy agents, including agents for replacing aberrant genes such as aberrant p53, or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy), cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme
- 15 or agents for increasing patient tolerance to chemotherapy or radiotherapy such as multi-drug resistant gene therapy; immunotherapy agents including *in vivo* and *ex vivo* approaches to increase the immunogenicity of patient tumour cells such as transfection with cytokines such as IL2, IL4 or GM-CSF, approaches to decrease T-cell anergy, approaches using
- 20 transfected immune cells such as cytokine-transfected dendritic cells or approaches using cytokine-transfected tumour cell lines or anti-idiotypic antibodies; corticosteroids such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate and mometasone furoate and hyaluronic acids such as hyalgan and synvisc and P2X7
- 25 receptor antagonists; drugs which promote Th1 cytokine response such as interferons, TNF or GM-CSF; other antagonists of PGD<sub>2</sub> acting at other receptors such as DP antagonists; inhibitors of phosphodiesterase type 4 such as cilonilast;
- 30 drugs that modulate cytokine production such as inhibitors of TNF $\alpha$  converting enzyme (TACE) anti-TNF monoclonal antibodies, TNF receptor immunoglobulin molecules, inhibitors of other TNF isoforms, non-selective COX-1/COX-2 inhibitors

such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac and apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin; COX-2 inhibitors such as meloxicam, celecoxib, fofecoxib, 5 valdecoxib and etoricoxib, low dose methotrexate, lefunomide, ciclesonide, hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold. drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors; PPAR- $\gamma$  agonists such as rosiglitazone; or with 10 anti-RSV antibodies such as Synagis (palivizumab) and agents that may be used to treat rhinovirus infection in the future e.g. interferon-beta and other interferons

15. A process for the preparation of a pharmaceutical composition as claimed in any one of claims 11 to 14 comprising bringing a compound as claimed in any one of 15 claims 1 to 6 in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle.

16. A product comprising a compound as claimed in any one of claims 1 to 6 and one or more of the agents listed in claim 14 as a combined preparation for 20 simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD<sub>2</sub> or other agonists at the CRTH2 receptor.

17. The use as claimed in claim 10, wherein the agent also comprises an additional active agent useful for the treatment of diseases and conditions mediated 25 by PGD<sub>2</sub> or other agonists at the CRTH2 and/or DP receptor.

18. The use as claimed in claim 17, wherein the additional active agent is one of the agents listed in claim 14.