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(54) **Indoles and their therapeutic use**

Indole und ihre therapeutische Verwendung

Indoles et leurs utilisation thérapeutiques

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Description

[0001] This invention relates to a class of indole compounds, which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2), and their use in the treatment of diseases responsive to modulation of CRTH2 receptor activity, principally diseases having a significant inflammatory component. The invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

Background to the Invention

[0002] Mast cells are known to play an important role in allergic and immune responses through the release of a number of mediators, such as histamine, leukotrienes, cytokines, prostaglandin D_2, etc (Boyce; Allergy Asthma Proc., 2004, 25, 27-30). Prostaglandin D_2 (PGD_2) is the major metabolite produced by the action of cyclooxygenase on arachadonic acid by mast cells in response to allergen challenge (Lewis et al; J. Immunol., 1982, 129, 1627-1631). It has been shown that PGD_2 production is increased in patients with systemic mastocytosis (Roberts; N. Engl. J. Med., 1980, 303, 1400-1404), allergic rhinitis (Naclerio et al; Am. Rev. Respir. Dis., 1983, 128, 597-602; Brown et al; Arch. Otolarynol. Head Neck Surg., 1987, 113, 179-183; Lebel et al; J. Allergy Clin. Immunol., 1988, 82, 869-877), bronchial asthma (Murray et al; N. Engl. J. Med., 1986, 315, 800-804; Liu et al; Am. Rev. Respir. Dis., 1990, 142, 126-132; Wenzel et al; J. Allergy Clin. Immunol., 1991, 87, 540-548), and urticaria (Heavey et al; J. Allergy Clin. Immunol., 1986, 78, 458-461). PGD_2 mediates it effects through two receptors, the PGD_2 (or DP) receptor (Boie et al; J. Biol. Chem., 1995, 270, 18910-18916) and the chemoattractant receptor-homologous molecule expressed on Th2 (or CRTH2) (Nagata et al; J. Immunol., 1999, 162, 1278-1289; Powell; Prostaglandins Luekot. Essent. Fatty Acids, 2003, 69, 179-185). Therefore, it has been postulated that agents that antagonise the effects of PGD_2 at its receptors may have beneficial effects in a number of disease states.

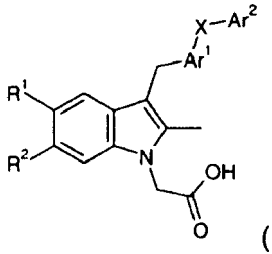
[0003] The CRTH2 receptor has been shown to be expressed on cell types associated with allergic inflammation, such as basophils, eosinophils, and Th2-type immune helper cells (Hirai et al, J. Exp. Med., 2001, 193, 255-261). The CRTH2 receptor has been shown to mediate PGD_2-mediated cell migration in these cell types (Hirai et al; J. Exp. Med., 2001, 193, 255-261), and also to play a major role in neutrophil and eosinophil cell recruitment in a model of contact dermatitis (Takeshita et al; Int. Immunol., 2004, 16, 947-959). Ramatroban ((3R)-3-[(4-fluorophenyl)sulphonylamino]-1,2,3,4-tetrahydro-9H-carbazole-9-propanoic acid}, a dual CRTH2 and thromboxane A_2 receptor antagonist, has been shown to attenuate these responses (Sugimoto et al;J. Pharmacol. Exp. Ther., 2003, 305, 347-352; Takeshita *et al; op. cit.*). The potential of PGD_2 both to enhance allergic inflammation and induce an inflammatory response has been demonstrated in mice and rats. Transgenic mice over expressing PGD_2 synthase exhibit an enhanced pulmonary eosinophilia and increased levels of Th2 cytokines in response to allergen challenge (Fujitani et al, J. Immunol., 2002, 168, 443-449). In addition, exogenously administered CRTH2 agonists enhance the allergic response in sensitised mice (Spik et al; J. Immunol., 2005, 174, 3703-3708). In rats exogenously applied CRTH2 agonists cause a pulmonary eosinophilia but a DP agonist (BW 245C) or a TP agonist (I-BOP) showed no effect (Shirashi et al; J. Pharmacol. Exp Ther., 2005, 312, 954-960). These observations suggest that CRTH2 antagonists may have valuable properties for the treatment of diseases mediated by PGD_2.

[0004] In addition to Ramatroban a number of other CRTH2 antagonists have been described. Examples include: indole acetic acids (WO2008/012511; WO2007/065684; WO2007/045867; WO2006/034419; WO2005/094816; WO2005/044260; WO2005/040114; WO2005/040112; GB2407318; WO2005/019171; WO2004/106302; WO2004/078719; WO2004/007451; WO2003/101981; WO2003/101961; WO20031097598; WO2003/097042; WO2003/066047; WO2003/066046; WO2003/022813), indolizine acetic acids (WO2008/113965; WO2008/074966; WO2007/031747; WO2006/136859), pyrrole acetic acids (WO2007/144127; WO2006/063763), quinolines (WO2008/122784; WO2008/119917; WO2007/036743), tetrahydroquinolines (WO2006/091674; US2005/256158; WO2005/100321; WO2005/007094; WO2004/035543; WO2004/032848; EP1435356; EP1413306), phenoxyacetic acids (WO2007/062678; WO2007/062773; WO2006/125596; WO2006/125593; WO2006/056752; WO2005/115382; WO2005/105727; WO2005/018529; WO2004/089885; WO2004/089884) and phenylacetic acids (WO2004/058164).

[0005] WO2006/095183 discloses compounds useful for the treatment of inflammatory disorders, including asthma, via modulation of CRTH2 receptor activity. One disclosed compound is {5-fluoro-2-methyl-3-[1-(phenylsulfonyl)pyrrol-2-ylmethyl]indol-1-yl}acetic acid.

Detailed Description of the Invention

[0006] According to one aspect of the present invention, novel compounds are of formula I



(I)

X is $-SO_2-$ or $*-SO_2NR^3-$ wherein the bond marked with an asterisk is attached to Ar^1;
R^1 is hydrogen, fluoro, chloro, CN or CF_3;
R^2 is hydrogen, fluoro or chloro;
R^3 is hydrogen, C_1-C_8alkyl or C_3-C_7cycloalkyl;
Ar^1 is a 5- or 6-membered heteroaryl group selected from furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from fluoro, chloro, CN, C_3-C_7cycloalkyl, $-O(C_1$-C_4alkyl) or C_1-C_6alkyl, the latter two groups being optionally substituted by one or more fluoro atoms;
Ar^2 is a 5- or 6-membered heteroaryl group selected from pyrrolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from fluoro, chloro, CN, C_3-C_7cycloalkyl, $-O(C_1$-C_4alkyl) or C_1-C_6alkyl, the latter two groups being optionally substituted by one or more fluoro atoms.

[0007] Compounds (I) with which the invention is concerned are CRTH2 receptor antagonists, but they may also have beneficial effects at other prostanoid receptors, such as the PGD_2 receptor or the thromboxane A_2 receptor.

[0008] Compounds of formula (I) above may be prepared or recovered in the form of salts, and in some cases as N-oxides, hydrates, and solvates thereof. Any reference herein, including the claims herein, to "compounds of the invention", "compounds with which the invention is concerned" or "compounds of formula (I)" and the like, includes reference to salts, particularly pharmaceutically acceptable salts, *N*-oxides, hydrates, and solvates of such compounds.

[0009] The invention also includes (i) use of a compound with which the invention is concerned in the manufacture of a medicament for use in the treatment of conditions responsive to modulation of CRTH2 receptor activity, and (ii) a method of treatment of conditions responsive to modulation of CRTH2 receptor activity, comprising administering to a patient suffering such disease an effective amount of a compound with which the invention is concerned.

[0010] Examples of conditions responsive to modulation of CRTH2 receptor activity include asthma, rhinitis, allergic airway syndrome, allergic rhinobronchitis, bronchitis, chronic obstructive pulmonary disease (COPD), nasal polyposis, sarcoidosis, farmer's lung, fibroid lung, cystic fibrosis, chronic cough, conjunctivitis, atopic dermatitis, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS dementia complex, Huntington's disease, frontotemporal dementia, Lewy body dementia, vascular dementia, Guillain-Barre syndrome, chronic demyelinating polyradiculoneurophathy, multifocal motor neuropathy, plexopathy, multiple sclerosis, encephalomyelitis, panencephalitis, cerebellar degeneration and encephalomyelitis, CNS trauma, migraine, stroke, rheumatoid arthritis, ankylosing spondylitis, Behçet's Disease, bursitis, carpal tunnel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, dermatomyositis, Ehlers-Danlos Syndrome (EDS), fibromyalgia, myofascial pain, osteoarthritis (OA), osteonecrosis, psoriatic arthritis, Reiter's syndrome (reactive arthritis), sarcoidosis, scleroderma, Sjogren's Syndrome, soft tissue disease, Still's Disease, tendinitis, polyarteritis Nodossa, Wegener's Granulomatosis, myositis (polymyositis dermatomyositis), gout, atherosclerosis, lupus erythematosus, systemic lupus erythematosus (SLE), type I diabetes, nephritic syndrome, glomerulonephritis, acute and chronic renal failure, eosinophilia fascitis, hyper IgE syndrome, sepsis, septic shock, ischemic reperfusion injury in the heart, allograft rejection after transplantations, and graft versus host disease.

[0011] However, the compounds with which the invention is concerned are primarily of value for the treatment of asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome, or allergic rhinobronchitis. Psoriasis, atopic and non-atopic dermatitis Crohn's disease, ulcerative colitis, and irritable bowel disease are other specific conditions where the present compounds may have particular utility.

[0012] Another aspect of the invention is a pharmaceutical composition comprising a compound with which the invention is concerned in admixture with a pharmaceutically acceptable carrier or excipient.

Terminology

[0013] As used herein, the term "(C_a-C_b)alkyl" wherein a and b are integers refers to a straight or branched chain alkyl radical having from a to b carbon atoms. Thus when a is 1 and b is 6, for example, the term includes methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl and *n*-hexyl.

[0014] As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0015] As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, for example sodium and potassium hydroxides; alkaline earth metal hydroxides, for example calcium, barium and magnesium hydroxides; with organic bases, for example *N*-methyl-D-glucamine, choline tris(hydroxymethyl) aminomethane, L-arginine, L-lysine, *N*-ethyl piperidine, dibenzylamine and the like. Specific salts with bases include the piperazine, ethanolamine, benzathine, calcium, diolamine, meglumine, olamine, potassium, procaine, sodium, tromethamine and zinc salts. Those compounds of the invention which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, for example with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids, for example acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, *p*-toluenesulphonic, benzoic, benzenesulfonic, glutamic, lactic and mandelic acids and the like. Where a compound contains a quaternary ammonium group acceptable counter-ions may be, for example chlorides, bromides, sulfates, methanesulfonates, benzenesulfonates, toluenesulfonates (tosylates), napadisylates (naphthalene-1,5-disulfonates or naphthalene-1-(sulfonic acid)-5-sulfonates), edisylates (ethane-1,2-disulfonates or ethane-1-(sulfonic acid)-2-sulfonates), isethionates 2-hydroxyethylsulfonates), phosphates, acetates, citrates, lactates, tartrates, mesylates, maleates, malates, fumarates, succinates, xinafoates, *p*-acetamidobenzoates and the like; wherein the number of quaternary ammonium species balances the pharmaceutically acceptable salt such that the compound has no net charge.

[0016] Salts are discussed in the "Handbook of Pharmaceutical Salts. Properties, selection and use", P. Heinrich Stahl & Camille G. Wermuth, Wiley-VCH, 2002.

[0017] The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

[0018] Compounds with which the invention is concerned may exist in one or more stereoisomeric form, because of the presence of asymmetric atoms or rotational restrictions, and in such cases can exist as a number of stereoisomers with R or S stereochemistry at each chiral centre or as atropisomers with R or S stereochemistry at each chiral axis. The invention includes all such enantiomers and diastereoisomers and mixtures thereof.

[0019] Use of prodrugs, such as esters, of compounds with which the invention is concerned is also part of the invention. "Prodrug" means a compound that is convertible *in vivo* by metabolic means (for example, by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyl-tartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluene-sulphonates, cyclohexylsulphamates and quinates. Examples of ester prodrugs are those described by F. J. Leinweber, Drug Metab. Res., 1987, 18, 379. As used in herein, references to the compounds of formula (I) are meant to also include the prodrug forms.

Structural aspects of compounds with which the invention is concerned

[0020] Subject to the proviso in the above definition of compounds with which the invention is concerned:

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

Ar^1 is a 5- or 6-membered heteroaryl group selected from furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl. In some cases, Ar^1 is thienyl, pyridinyl, pyrimidinylimidazolyl, isothiazolyl or thiazolyl.

Ar^2 is a 5- or 6-membered heteroaryl. Examples of such rings include pyrrolyl, imidazolyl, furanyl, thienyl, oxazolyl, thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyrazinyl, pyrimidinyl and pyridazinyl. In some cases, Ar^2 is pyridinyl, thienyl or pyrimidinyl.

[0021] In one particular subclass of compounds of the invention, X is *-SO_2NR^3- wherein the bond marked with an

asterisk is attached to Ar^1.

[0022] Ar^1 and Ar^2 may be optionally be substituted by one or more substituents independently selected from fluoro, chloro, CN, C_3-C_7cycloalkyl such as cyclopropyl, O(C_1-C_4alkyl) such as methoxy, C_1-C_6alkyl such as methyl or the latter two groups being optionally substituted by one or more fluoro atoms, as in the case of trifluormethoxy or trifluoromethyl. Currently preferred such substituents are chloro, fluoro, CN and methyl.

[0023] The radical Ar^2SO_2- or $Ar^2N(R^3)SO_2$- may be in the meta- or para-position of the ring Ar^1 relative to the point of attachment of Ar^1 to the rest of the molecule.

[0024] However, currently it is preferred that the radicals Ar^2SO_2- or $Ar^2SO_2NR^3$- are in the ortho-position of the ring Ar^1 relative to the point of attachment of Ar^1 to the rest of the molecule.

[0025] Specific compounds of the invention include those of the Examples herein.

Compositions

[0026] As mentioned above, the compounds with which the invention is concerned are CRTH2 receptor antagonists, and are useful in the treatment of diseases, which benefit from such modulation. Examples of such diseases are referred to above, and include asthma, rhinitis, allergic airway syndrome, bronchitis and chronic obstructive pulmonary disease.

[0027] It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing treatment. Optimum dose levels and frequency of dosing will be determined by clinical trial, as is required in the pharmaceutical art. In general, the daily dose range will lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, often 0.01 mg to about 50 mg per kg, for example 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

[0028] The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulfate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

[0029] For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations, which may be used for the drug, are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

[0030] The drug may also be formulated for inhalation, for example as a nasal spray, or dry powder or aerosol inhalers. For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation. Aerosol generation can be carried out using, for example, pressure-driven jet atomizers or ultrasonic atomizers, preferably using propellant-driven metered aerosols or propellant-free administration of micronized active compounds from, for example, inhalation capsules or other "dry powder" delivery systems.

[0031] The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

[0032] Other compounds may be combined with compounds with which the invention is concerned for the prevention and treatment of prostaglandin-mediated diseases. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating PGD_2-mediated diseases comprising a therapeutically effective amount of a compound of the invention and one or more other therapeutic agents. Suitable therapeutic agents for a combination therapy with compounds of the invention include, but are not limited to: (1) corticosteroids, such as fluticasone, ciclesonide or budesonide; (2) β2-adrenoreceptor agonists, such as salmeterol, indacaterol or formoterol; (3) leukotriene modulators, for example leukotriene antagonists such as montelukast, zafirulast or pranlukast or leukotriene biosynthesis inhibitors such as Zileuton or BAY-1005; (4) anticholinergic agents, for example muscarinic-3 (M3) receptor antagonists such as

tiotropium bromide; (5) phosphodiesterase-IV (PDE-IV) inhibitors, such as roflumilast or cilomilast; (6) antihistamines, for example selective histamine-1 (H1) receptor antagonists, such as fexofenadine, citirizine, loratidine or astemizole; (7) antitussive agents, such as codeine or dextramorphan; (8) non-selective COX-1 / COX-2 inhibitors, such as ibuprofen or ketoprofen; (9) COX-2 inhibitors, such as celecoxib and rofecoxib; (10) VLA-4 antagonists, such as those described in WO97/03094 and WO97/02289; (11) TACE inhibitors and TNF-α inhibitors, for example anti-TNF monoclonal antibodies, such as Remicade and CDP-870 and TNF receptor immunoglobulin molecules, such as Enbrel; (12) inhibitors of matrix metalloprotease, for example MMP12; (13) human neutrophil elastase inhibitors, such as those described in WO2005/026124, WO2003/053930 and WO06/082412; (14) A2a agonists such as those described in EP1052264 and EP1241176 (15) A2b antagonists such as those described in WO2002/42298; (16) modulators of chemokine receptor function, for example antagonists of CCR3 and CCR8; (17) compounds which modulate the action of other prostanoid receptors, for example a thromboxane A_2 antagonist; and (18) agents that modulate Th2 function, such as PPAR agonists.

[0033] The weight ratio of the compound of the invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

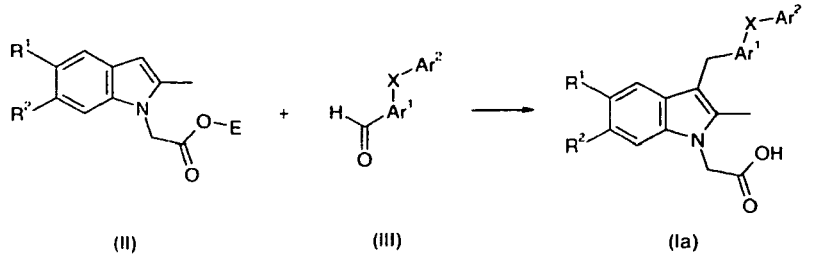
Synthesis

[0034] There are multiple synthetic strategies for the synthesis of the compounds with which the present invention is concerned, but all rely on chemistry known to the synthetic organic chemist. Thus, compounds of the invention can be synthesised according to procedures described in the standard literature and are well-known to the one skilled in the art. Typical literature sources are "Advanced organic chemistry', 4th Edition (Wiley), J. March, "Comprehensive Organic Transformation", 2nd Edition (Wiley), R. C. Larock, "Handbook of Heterocyclic Chemistry', 2nd Edition (Pergamon), A. R. Katritzky, review articles such as found in *"Synthesis", "Acc. Chem. Res.", "Chem. Rev.",* or primary literature sources identified by standard literature searches online or from secondary sources such as *"Chemical Abstracts"* or *"Beilstein".* The extensive literature relating to the synthesis of indole compounds is especially relevant, of course.

[0035] It may be necessary to protect reactive functional groups (for example, hydroxy, amino, thio or carboxy) in intermediates used in the preparation of compounds of formula (I) to avoid their unwanted participation in a reaction leading to the formation of compounds of formula (I). Conventional protecting groups, for example those described by T. W. Greene and P. G. M. Wuts in "Protective groups in organic chemistry" John Wiley and Sons, 1999, may be used.

[0036] The compounds of the invention of formula (I) may be isolated in the form of their pharmaceutically acceptable salts, such as those described previously herein above. The free acid form corresponding to isolated salts can be generated by acidification with a suitable acid such as acetic acid and hydrochloric acid and extraction of the liberated free acid into an organic solvent followed by evaporation. The free acid form isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate base and subsequent evaporation, precipitation, or crystallisation.

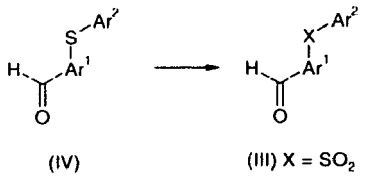
[0037] Compounds of formula (Ia), wherein X, R^1, R^2, Ar^1 and Ar^2 are as defined for formula (I) above, may conveniently be prepared by the reaction between an indole of formula (II), wherein E represents hydrogen or alkyl group, and an aldehyde of formula (III) (Scheme 1). The reaction is carried out under acidic reductive conditions, for example a mixture of trifluoroacetic acid and triethylsilane. It is to be understood that if the reaction is carried out on a protected form of (II) an appropriate deprotection step will be required to obtain the desired compound of the invention (Ia). Compounds of formula (II) are commercially available or can be prepared by known methods (Kim et al; J. Heterocycl. Chem., 1981, 18, 1365-71; Forbes et al; Syn. Commun., 1996, 26, 745-754).



(II) (III) (Ia)

Scheme 1

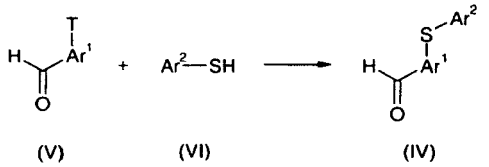
[0038] Intermediate compounds of formula (III), wherein X represents SO_2 group, may be prepared by the oxidation of compounds of formula (IV), with a suitable oxidising agent such as potassium peroxymonosulfate, *meta*-chloroperoxybenzoic acid or other well known oxidising agents (Scheme 2).



(IV) (III) X = SO_2

Scheme 2

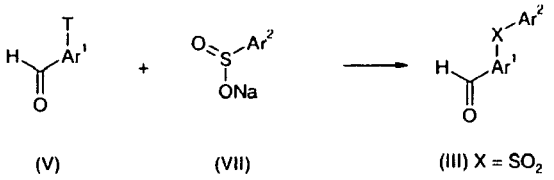
[0039] Compounds of formula (IV) may be prepared from compounds of formula (V), wherein T represents a chloro, bromo, or iodo atom, or a trifluoromethanesulfonyloxy group, by reaction with a thiol of formula (VI) in the presence of a suitable base such as potassium carbonate (Scheme 3). Alternatively, the reaction may be carried out in the presence of a suitable catalyst, such as tetrakis(triphenylphosphine)palladium(0) in a protic solvent such as ethanol. Compounds of formula (V) and (VI) are commercially available or can be prepared by known methods.



(V) (VI) (IV)

Scheme 3

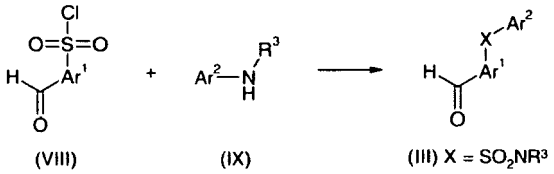
[0040] Alternatively, intermediate compounds of formula (III), wherein X represents SO_2 group, may be prepared by reaction of compounds of formula (V) and (VII) (Scheme 4). The reaction may be carried out in a suitable solvent such as dimethyl sulfoxide, at temperatures ranging from room temperature to 150°C. Compounds of formula (VII) are commercially available or can be prepared by known methods.



(V) (VII) (III) X = SO_2

Scheme 4

[0041] Intermediate compounds of formula (III), wherein X represents SO_2NR^3 group, may be prepared by the reaction between a compound of formula (VIII) and an amine of formula (IX) (Scheme 5). The reaction may be carried out in the presence of a suitable base (for example, triethylamine or diisopropylethylamine) and solvent (for example, dichloromethane or dichloroethane), at temperatures ranging from 0°C to the reflux temperature of the solvent, preferably at about room temperature. Compounds of formula (VIII) and (IX) are commercially available or can be prepared by known methods.



(VIII) (IX) (III) X = SO_2NR^3

Scheme 5

Examples

[0042] ^{1}H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5 mm probe spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations have been used: br s = broad singlet, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

[0043] Mass Spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using the following methods:

Method A: experiments were performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 μm 100 x 3.0 mm column and a 2 mL / minute flow rate. The initial solvent system was 95% water containing 0.1% formic acid (solvent A) and 5% acetonitrile containing 0.1% formic acid (solvent B) for the first minute followed by a gradient up to 5% solvent A and 95% solvent B over the next 14 minutes. The final solvent system was held constant for a further 2 minutes.

[0044] Microwave experiments were carried out using a Personal Chemistry Smith Synthesizer™, which uses a single-mode resonator and dynamic field tuning, both of which give reproducibility and control. Temperatures from 40-250°C can be achieved, and pressures of up to 20 bars can be reached. Two types of vial are available for this processor, 0.5-2.0 mL and 2.0-5.0 mL.

[0045] Reverse-phase preparative HPLC purifications were carried out using Genesis 7 micron C-18 bonded silica stationary phase in columns 10 cm in length and 2 cm internal diameter. The mobile phase used was mixtures of acetonitrile and water (both buffered with 0.1% v/v trifluoroacetic acid or formic acid) with a flow rate of 10 mL per minute and typical gradients of 40 to 90% organic modifier ramped up over 30 to 40 minutes. Fractions containing the required product (identified by LCMS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the final product.

[0046] Preparations A to H are provided for reference.

Preparation A: {5-fluoro-3-[3-(4-fluorobenzenesulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid methyl ester

[0047] A mixture of triethylsilane (0.79 g), trifluoroacetic acid (0.47 g) and 1,2-dichloroethane (2.0 mL) at -10°C was treated dropwise with a mixture of (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester (0.1 g), 3-(4-fluorobenzenesulfonyl)thiophene-2-carbaldehyde (0.15 g) and 1,2-dichloroethane (3.0 mL), and the resulting mixture was stirred at -10°C for 15 minutes and then at room temperature overnight. The mixture was diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:1 to 0:1 by volume) to afford the title compound as a colourless gum (0.17 g).
^{1}H NMR ($CDCl_3$): δ 2.2 (s, 3H), 3.76 (s, 3H), 4.44 (s, 2H), 4.81 (s, 2H), 6.66 (dd, J = 2.5, 9.4 Hz, 1H), 6.87-6.91 (m, 1H), 7.05-7.10 (m, 2H), 7.23 (t, J = 8.6 Hz, 2H), 7.41 (d, J = 5.4 Hz, 1H), 8.00 (dd, J = 5.4, 8.9 Hz, 2H).

Preparation B: 3-(4-fluorobenzenesulfonyl)pyridine-4-carbaldehyde

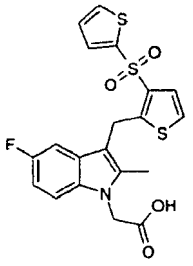
[0048] A solution of 3-fluoroisonicotinaldehyde (0.25 mL) in dimethyl sulfoxide (2.0 mL) was treated with a solution of 4-fluorobenzene sulfinic acid sodium salt (0.5 g) in dimethyl sulfoxide (3.0 mL), and the resulting mixture was stirred at 100°C for 3 days. The mixture was cooled to room temperature, partitioned between water and ethyl acetate (20 mL), and the aqueous phase extracted with ethyl acetate. The combined organic solution was dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:0 to 4:1 by volume) to afford the title compound as a white solid (0.38 g).

Preparation C: 3-(4-fluorobenzenesulfonyl)pyridine-2-carbaldehyde

[0049] A mixture of 3-fluoropyridine-2-carbaldehyde (0.70 g), 4-fluorobenzenesulfinic acid sodium salt (1.1 g) and dimethyl sulfoxide (7.0 mL) was stirred at 100°C for 18 hours. The mixture was cooled to room temperature, diluted with water (20 mL), and the resulting precipitate was removed by filtration. The filtrate was extracted with ethyl acetate, and the combined organic extract was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a pale yellow oil (0.67 g).
^{1}H NMR ($CDCl_3$): δ 7.23 (m, 2H), 7.22 (dd, J = 4.7, 8.0 Hz, 1H), 8.03 (m, 2H), 8.63 (ddd, J = 0.3, 1.5, 8.0 Hz, 1H), 8.97 (dd, J = 1.5, 4.7 Hz, 1H), 10.36 (s, 1H).

Example 1: {5-fluoro-2-methyl-3-[3-(thiophene-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0050]



Preparation 1a: 3-(thiophen-2-ylsulfanyl)thiophene-2-carbaldehyde

[0051] A mixture of 3-chlorothiophene-2-carbaldehyde (1.0 g), potassium carbonate (2.8 g) and *N,N*-dimethylformamide (6.8 mL) was treated dropwise with thiophene-2-thiol (0.87 g), and the resulting mixture was stirred at room temperature for 3 hours. The mixture was poured onto water (150 mL) and extracted with diethyl ether. The combined organic extract was washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution, and then dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a red oil (1.5 g).
^{1}H NMR ($CDCl_3$): δ 6.72 (d, J = 5.3 Hz, 1H), 7.09 (dd, J = 3.5, 5.6 Hz, 1H), 7.34 (dd, J = 1.3, 3.5 Hz, 1H), 7.52 (dd, J = 1.3, 5.3 Hz, 1H), 7.58 (dd, J = 0.9, 5.2 Hz, 1H), 10.09 (d, J = 1.0 Hz, 1H).
MS: ESI (+ve) (Method B): Retention time 3.6 min.

Preparation 1b: 3-(thiophene-2-sulfonyl)thiophene-2-carbaldehyde

[0052] A mixture of 3-(thiophen-2-ylsulfanyl)thiophene-2-carbaldehyde (1.5 g) and dichloromethane (68 mL) was treated with 3-chloroperoxybenzoic acid (70% in water, 4.6 g), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was diluted with saturated aqueous sodium thiosulfate solution (50 mL), extracted with diethyl ether and the combined organic extract was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, and then dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a brown solid (1.2 g).
^{1}H NMR ($CDCl_3$): δ 7.15 (dd, J = 3.8, 5.1 Hz, 1H), 7.53 (d, J = 5.3 Hz, 1 H), 7.70 (dd, J = 1.3, 5.1 Hz, 1 H), 7.75 (dd, J = 1.3, 4.8 Hz, 1H), 7.77 (dd, J = 1.4, 3.8 Hz, 1 H), 10.66 (d, J = 1.3 Hz).
MS: ESI (+ve) (Method B): Retention time 3.3 min.

Preparation 1c: {5-fluoro-2-methyl-3-[3-(thiophene-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester

[0053] A mixture of (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester (0.14 g), 3-(thiophene-2-sulfonyl)thiophene-2-carbaldehyde (0.12 g) and dichloroethane (5.0 mL) at 0°C was treated dropwise with a mixture of triethylsilane (1.4 mL), trifluoroacetic acid (0.35 mL) and dichloroethane (2.0 mL), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was cooled to 0°C, diluted with saturated aqueous sodium hydrogen carbonate solution and the phases separated. The aqueous phase was extracted with dichloromethane and the combined organic solution was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 1:1 by volume), to afford the title compound as a yellow solid (0.17 g).
1H NMR (DMSO-d_6): δ 2.23 (s, 3H), 3.68 (s, 3H), 4.50 (s, 2H), 5.12 (s, 2H), 6.83 (dd, J = 2.5, 9.7 Hz, 1H), 6.89 (ddd, J = 2.5, 9.2, 9.2 Hz, 1H), 7.28 (dd, J = 3.8, 4.9 Hz, 1H), 7.36 (d, J = 5.6 Hz, 1H), 7.39 (dd, J = 4.3, 9.0 Hz, 1H), 7.44 (d, J = 5.6 Hz, 1H), 7.95 (dd, J = 1.5, 3.8 Hz, 1H), 8.13 (dd, J = 1.5, 4.8 Hz, 1H).
MS: ESI (+ve) (Method B): 464 $(M+H)^+$, Retention time 3.9 min.

Preparation 1d: (5-fluoro-2-methyl-3-[3-(thiophene-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0054] A mixture of {5-fluoro-2-methyl-3-[3-(thiophene-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester (0.17 g), tetrahydrofuran (0.35 mL) and water (0.35 mL) was treated with lithium hydroxide (0.088 g), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was cooled to 0°C. pH adjusted to 5 by the addition of

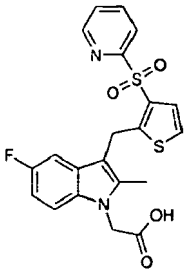
1.0 M aqueous hydrochloric acid solution and extracted with ethyl acetate. The combined organic extract was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC, eluting with a mixture of acetonitrile and water (3:7 to 9:1 by volume) to afford the title compound as a white solid (0.089 g).

^{1}H NMR (DMSO-d_6): δ 2.19 (s, 3H), 4.46 (s, 2H), 4.93 (s, 2H), 6.77 (dd, J = 2.6, 9.8 Hz, 1H), 6.83 (ddd, J = 2.5, 9.2, 9.2 Hz, 1H), 7.24 (dd, J = 4.0, 4.8 Hz), 7.31 (d, J = 5.5 Hz), 7.34 (dd, J = 4.4, 4.4 Hz), 7.39 (d, J = 5.4 Hz, 1H), 7.91 (dd, J=1.3, 3.5 Hz, 1H), 8.09 (dd, J = 1.3, 4.9 Hz, 1H), 12.96 (br s, 1H).

MS: ESI (+ve) (Method A): 450 $(M+H)^+$, Retention time 10.7 min.

Example 2: {5-fluoro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2 ylmethyl] indol-1-yl}acetic acid

[0055]



Preparation 2a: 3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde

[0056] The title compound was prepared by the method of Preparation B using 2-formyl-3-chlorothiophene and pyridine-2-sulfinic acid sodium salt.

^{1}H NMR ($CDCl_3$): δ 7.52 (ddd, J = 1.2, 4.6, 7.5 Hz, 1H), 7.58 (d, J = 5.2 Hz, 1H), 7.69 (dd, J = 1.2, 5.2 Hz, 1H), 7.98 (td, J = 1.7, 7.8 Hz, 1H), 8.24 (dt, J = 1.0, 7.9 Hz, 1 H), 8.70 (ddd, J = 0.9, 1.7, 4.7 Hz, 1 H), 10.70 (d, J = 1.2 Hz, 1 H).

Preparation 2b: {5-fluoro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester

[0057] The title compound was prepared by the method of Preparation A using 3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde and (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 3.76 (s, 3H), 4.71 (s, 2H), 4.81 (s, 2H), 6.82-6.95 (m, 2H), 7.01-7.10 (m, 2H), 7.41 (d, J = 5.4 Hz, 1H), 7.53 (ddd, J = 1.2, 4.7, 7.7 Hz, 1 H), 7.96 (td, J = 1.8. 7.8 Hz, 1H), 8.21 (dt, J = 1.0, 7.9 Hz, 1 H), 8.79 (ddd, J = 0.9, 1.7, 4.7 Hz, 1H).

Preparation 2c: {5-fluoro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl] indol-1-yl}acetic acid

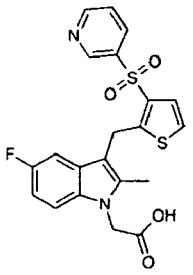
[0058] A solution of {5-fluoro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester (0.050 g) in tetrahydrofuran (0.30 mL) was treated with 1.0 M aqueous lithium hydroxide solution (1.0 mL), and the resulting mixture was stirred at room temperature overnight. The mixture was treated with 5.0 M aqueous sodium hydroxide solution (1.0 mL) and stirred at room temperature for 3 hours and then at 40°C overnight. The mixture was acidified by the addition of aqueous hydrochloric acid solution and concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC, eluting with a mixture of acetonitrile and water (2:3 to 19:1 by volume) to afford the title compound as a yellow solid (0.020 g).

^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H), 4.50 (s, 2H), 4.89 (s, 2H), 6.82 (m, 2H), 7.27-7.33 (m, 2H), 7.37 (d, J = 5.4 Hz, 1H), 7.71 (ddd, J = 1.2, 4.7, 7.6 Hz, 1H), 8.13 (td, J = 1.8, 7.8 Hz, 1H), 8.19 (dt, J = 1.1, 7.7 Hz, 1H), 8.73 (ddd, J = 0.9, 1.7, 4.7 Hz, 1H), 12.96 (br s, 1H).

MS: ESI (+ve) (Method A): 445 $(M+H)^+$, Retention time 9.9 min.

Example 3: {5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid

[0059]



Preparation 3a: 3-(pyridine-3-sulfonyl)thiophene-2-carbaldehyde

[0060] A mixture of 3-chlorothiophene-2-carbaldehyde (0.16 g), pyridine-3-sulfinic acid sodium salt (0.30 g) and dimethyl sulfoxide (2.0 mL) was heated at 80°C for 3 hours and then at 90°C for 3 hours. The mixture was diluted with water, extracted with ethyl acetate and the combined organic extract was dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a grey solid (0.079 g).
^{1}H NMR ($CDCl_3$): δ 7.50-7.57 (m, 2H), 7.75 (dd, J = 1.2, 5.2 Hz, 1H), 8.23-8.28 (m, 1 H), 8.88 (s, 1 H), 9.20 (s, 1 H), 10.64 (d, J = 1.2 Hz, 1 H).

Preparation 3b: {5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid methyl ester

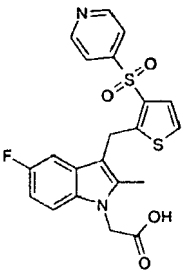
[0061] A mixture of triethylsilane (0.42 g), trifluoroacetic acid (0.25 g) and 1,2-dichloroethane (2.0 mL) at -10°C was treated dropwise with a mixture of (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester (0.055 g), 3-(pyridine-3-sulfonyl) thiophene-2-carbaldehyde (0.075 g) and 1,2-dichloroethane (2.0 mL), and the resulting mixture was stirred at room temperature for 20 hours. The mixture was treated with additional triethylsilane (0.42 g) and trifluoroacetic acid (0.25 g), and stirred at room temperature for 3 hours and then at 50°C for 20 hours. The mixture was diluted with dichloromethane, washed with saturated aqueous sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with a mixture of diethyl ether and ethyl acetate (1:0 to 0:1 by volume), followed by trituration with diethyl ether to afford the title compound as a white solid (0.027 g).
^{1}H NMR ($CDCl_3$): δ 2.26 (s, 3H), 3.72 (s, 3H), 4.43 (s, 2H), 4.77 (s, 2H), 6.67 (dd, J = 2.4, 6.9 Hz, 1H), 6.83 (dt, J = 2.5, 9.0 Hz, 1H), 7.03 (dd, J = 4.2, 8.8 Hz, 1H), 7.07 (d, J = 5.7 Hz, 1H), 7.39-7.45 (m, 2H), 8.14-8.18 (m, 1H), 8.79 (d, J=4.5 Hz, 1H), 9.13 (s, 1H).

Preparation 3c: {5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid

[0062] A mixture of {5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid methyl ester (0.025 g) and tetrahydrofuran (0.8 mL) was treated with 2.0 M aqueous sodium hydroxide solution (0.5 mL), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was acidified by the addition of 1.0 M aqueous hydrochloric acid solution, extracted with ethyl acetate and the combined organic extract was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue triturated with diethyl ether to afford the title compound as a white solid (0.020 g).
^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H), 4.45 (s, 2H), 4.92 (s, 2H), 6.72 (dd, J = 2.5, 9.8 Hz, 1H), 6.82 (td, J = 2.6, 9.1 Hz, 1H), 7.32 (dd, J = 4.4, 8.8 Hz, 1H), 7.40-7.44 (m, 2H), 7.63 (dd, J = 4.8, 8.1 Hz, 1H), 8.35-8.39 (m, 1H), 8.85 (dd, J =1.8, 4.9 Hz, 1H), 9.13-9.16 (m, 1H), 12.98 (br s, 1H).
MS: ESI (+ve) (Method A): 445 $(M+H)^+$, Retention time 9.5 min.

Example 4: {5-fluoro-2-methyl-3-[3-(pyridine-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0063]



Preparation 4a: 3-(pyridin-4-ylsulfanyl)thiophene-2-carbaldehyde

[0064] A mixture of 4-mercaptopyridine (1.0 g), potassium carbonate (3.7 g) and dimethyl sulfoxide (10 mL) at 0°C was treated with 3-chlorothiophene-2-carbaldehyde (1.3 g), and the resulting mixture was stirred at room temperature for 20 hours. The mixture was partitioned between ethyl acetate and water, and the organic phase was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and petroleum ether (1:9 to 3:2 by volume) to afford the title compound as yellow oil (1.3 g).
^{1}HNMR ($CDCl_3$) δ 7.01 (m, 2H), 7.16 (d, J = 5.0 Hz, 1H), 7.85 (dd, J = 1.3, 5.0 Hz, 1H), 8.44 (d, J = 5.0 Hz, 2H), 10.12 (s, 1H).

Preparation 4b: {5-fluoro-2-methyl-3-[3-(pyridin-4-ylsulfanyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester

[0065] A mixture of 3-(pyridin-4-ylsulfanyl)thiophene-2-carbaldehyde (1.3 g), (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester (1.3 g) and 1,2-dichloroethane (30 mL) at -10°C was treated with a mixture of triethylsilane (5.8 mL), trifluoroacetic acid (2.4 mL) and 1,2-dichloroethane (20 mL), and the resulting mixture was stirred at room temperature for 48 hours. The mixture was diluted with dichloromethane, washed with aqueous sodium bicarbonate solution and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with ethyl acetate to afford the title compound as yellow foam (2.4 g).
^{1}HNMR ($CDCl_3$) δ 2.28 (s, 3H), 3.73 (s, 3H), 4.21 (s, 2H), 4.69 (s, 2H), 6.81 (dd, J = 1.6, 4.5 Hz, 2H), 6.87 (m, 1H), 7.02 (m, 2H), 7.08 (dd, J = 2.4, 9.5 Hz, 1H), 7.20 (d, J = 5.3 Hz, 1H), 8.28 (dd, J = 1.6, 4.6 Hz, 2H).

Preparation 4c: {5-fluoro-2-methyl-3-[3-(pyridine-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester

[0066] A mixture of 5-fluoro-2-methyl-3-[3-(pyridin-4-ylsulfanyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester (0.20 g) and dichloromethane (2 mL) at 0°C was treated dropwise with a solution of 3-chloroperoxybenzoic acid (0.16 g) in dichloromethane (0.5 mL), and the resulting mixture was stirred at room temperature for 18 hours. The mixture was cooled to 0°C, treated with additional 3-chloroperoxybenzoic acid (0.16 g) and stirred at 0°C temperature for 1 hour. The mixture was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was dried over sodium sulfate and concentrated under reduced pressure to afford a brown oil. The residue was purified by column chromatography on a silica gel, eluting with a mixture of dichloromethane and ethyl acetate (9:1 to 0:10 by volume). Further purification by preparative reverse-phase HPLC, eluting with a mixture acetonitrile and water (1:9 to 9:1 by volume) gave the title compound as a yellow solid (0.026 g).
MS: ESI (+ve) (Method B): 459 $(M+H)^+$, Retention time 2.4 min.

Preparation 4d: {5-fluoro-2-methyl-3-[3-(pyridine-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0067] A mixture of {5-fluoro-2-methyl-3-[3-(pyridine-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester (0.026 g) and tetrahydrofuran (0.5 mL) was treated with 2.0 M aqueous sodium hydroxide solution (2.0 mL), and the resulting mixture was stirred at room temperature for 3 hours. The mixture was acidified by the addition of 2.0 M aqueous hydrochloric acid solution and concentrated under reduced pressure. The residue was purified by preparative HPLC, eluting with a mixture of acetonitrile and water (1:19 to 1:1 by volume) to afford the title compound as yellow solid (0.015 g).
^{1}HNMR ($CDCl_3$) δ 1.76 (s, 3H), 3.39 (d, J = 17.0 Hz, 1H), 4.39 (d, J = 17.7 Hz, 1H), 4.52 (d, J = 17.7 Hz, 1H), 4.56 (d, J = 17.0 Hz, 1H), 6.90 (m, 2H), 7.11 (d, J = 5.3 Hz, 1H), 7.22 (m, 1H), 7.42 (dd, J = 8.3, 2.9 Hz, 1H), 7.49 (d, J = 5.3 Hz, 1H), 7.63 (dd, J = 8.7, 5.0 Hz, 1H), 8.30 (m, 2H).
MS: ESI (+ve) (Method A): 445 $(M+H)^+$, Retention time 6.1 min.

Preparation D: [3-(3-benzenesulfonylthiophen-2-ylmethyl)-5-chloro-2-methylindol-1-yl]acetic acid methyl ester

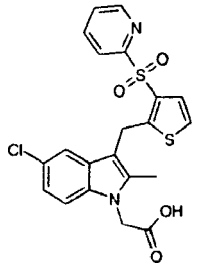
[0068] A mixture of triethylsilane (2.7 g), trifluoroacetic acid (1.6 g) and dichloroethane (8.0 mL) at -20°C was treated dropwise with a mixture of (5-chloro-2-methylindol-1-yl)acetic acid methyl ester (0.36 g), 3-phenylsulphony-2-thiophenealdehyde (0.39 g) and dichloroethane (8.0 mL), and the resulting mixture was warmed to room temperature over a period of 1.5 hours. The mixture was treated with additional triethylsilane (2.7 g) and trifluoroacetic acid (1.6 g) and then stirred at room temperature for 1 hour. The mixture was diluted with saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic extract was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:0 to 0:1 by volume) to afford the title compound (0.55 g).
MS: ESI (+ve) (Method B): 474 $(M+H)^+$, Retention time 4.1 min.

Preparation E: [3-(3-benzenesulfonylthiophen-2-ylmethyl)-5-chloro-2-methylindol-1-yl]acetic acid

[0069] A mixture of [3-(3-benzenesulfonylthiophen-2-ylmethyl)-5-chforo-2-methylindol-1-yl] acetic acid methyl ester (0.47 g), 1.0 M aqueous lithium hydroxide solution (2.0 mL) and tetrahydrofuran (2.0 mL) was stirred at room temperature for 1 hour. The mixture was acidified with 1.0 M aqueous hydrochloric acid solution and extracted with ethyl acetate. The combined organic extract was dried using a phase separation cartridge and concentrated under reduced pressure. The residue was purified by crystallisation from a mixture of pentane and ethyl acetate to afford the title compound as a white powder (0.39 g).
^{1}H NMR (DMSO-d_6): δ 2.17 (s, 3H), 4.41 (s, 2H), 4.93 (s, 2H), 6.88 (d, J = 2.0 Hz, 1H), 6.98 (dd, J = 2.0, 8.7 Hz, 1H), 7.33 (s, 1H), 7.35 (d, J = 5.5 Hz, 1H), 7.39 (d, J = 5.5 Hz, 1H), 7.61-7.67 (m, 2H), 7.69-7.74 (m, 1H), 7.98-8.02 (m, 2H).
MS: ESI (+ve) (Method A): 459 $(M+H)^+$, Retention time 11.2 min.

Example 5: {5-chloro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0070]



Preparation 5a: 3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde

[0071] A mixture of pyridine-2-sulfinate sodium salt (8.5 g), 3-bromothiophene-2-carbaldehyde (6.5 g) and dimethyl sulfoxide (50 mL) (split equally into four microwave vials) was heated by microwave irradiation at 125°C for 45 minutes. The combined mixtures were diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:0 to 0:1 by volume) to afford the title compound as a yellow solid (0.55 g).
^{1}H NMR ($CDCl_3$): δ 7.52 (ddd, J = 0.8, 4.7, 7.7 Hz, 1H), 7.58 (d, J = 5.2 Hz, 1H), 7.69 (dd, J = 1.0, 4.2 Hz, 1H), 7.98 (dt, J = 1.7, 7.8 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.70 (d, J = 4.7 Hz, 1H), 10.7 (d, J = 1.0 Hz 1H).

Preparation 5b: {5-chloro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl] indol-1-yl}acetic acid methyl ester

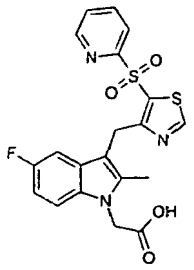
[0072] The title compound was prepared by the method of Preparation D using 3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde and (5-chloro-2-methylindol-1-yl)acetic acid methyl ester.
MS: ESI (+ve) (Method B): 475 $(M+H)^+$, Retention time 3.9 min.

Preparation 5c: {5-chloro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl] indol-1-yl}acetic acid

[0073] The title compound was prepared by the method of Preparation E using {5-chloro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester.
^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H), 4.52 (s, 2H), 4.93 (s, 2H), 6.99 (dd, J = 2.1, 8.7 Hz, 1H), 7.06 (dd, J = 2.0 Hz, 1H), 7.29 (d, J = 5.3 Hz, 1H), 7.35 (d, J = 8.7 Hz, 1H), 7.38 (d, J = 5.3 Hz, 1H), 7.72 (ddd, J = 1.2, 4.6, 7.6 Hz, 1H), 8.13 (dt, J = 1.7, 7.8 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.76 (m, 1H).
MS: ESI (+ve) (Method A): 461 $(M+H)^+$, Retention time 10.4 min.

Example 6: {5-fluoro-2-methyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylmethyl] indol-1-yl}acetic acid

[0074]



Preparation 6a: 5-(pyridine-2-sulfonyl)thiazole-4-carbaldehyde

[0075] The title compound was prepared by the method of Preparation B using 5-chloro-thiazole-4-carbaldehyde and pyridine-2-sulfinic acid sodium salt.
MS: ESI (+ve) (Method B): 257 $(M+H)^+$, Retention time 2.1 min.

Preparation 6b: {5-fluoro-2-methyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylmethyl]indol-1-yl}acetic acid methyl ester

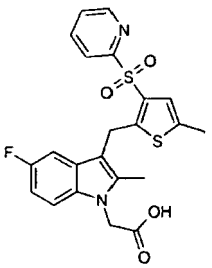
[0076] The title compound was prepared by the method of Preparation A using (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester and 5-(pyridine-2-sulfonyl)thiazole-4-carbaldehyde.
MS: ESI (+ve) (Method B): 460 $(M+H)^+$, Retention time 3.6 min.

Preparation 6c: {5-fluoro-2-methyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylmethyl]indol-1-yl}acetic acid

[0077] The title compound was prepared by the method of Preparation E using {5-fluoro-2-methyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylmethyl]indol-1-yl}acetic acid methyl ester.
^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H), 4.34 (s, 2H), 4.83 (s, 2H), 6.75 (m, 2H), 7.19 (dd, J = 4.4, 8.8 Hz, 1H), 7.62 (ddd, J = 1.4, 4.7, 7.3 Hz, 1H), 8.00-8.09 (m, 2H), 8.59-8.62 (m, 1H), 9.30 (s, 1H), 12.9 (br s, 1H).
MS: ESI (+ve) (Method A): 446 $(M+H)^+$, Retention time 9.3 min.

Example 7: {5-fluoro-2-methyl-3-[5-methyl-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid

[0078]



Preparation 7a: 5-methyl-3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde

[0079] The title compound was prepared by the method of Preparation C using 3-bromo-5-methylthiophene-2-carbaldehyde and pyridine-2-sulfinate sodium salt.
^{1}H NMR (DMSO-d_6): δ 2.54 (d, J = 1.0 Hz, 3H), 7.49-7.53 (m, 1H), 7.97 (td, J = 1.7, 7.8, Hz, 1H), 8.21 (dt, J = 1.0, 7.9, Hz, 1H), 8.70 (ddd, J = 0.9, 1.7, 4.7 Hz, 1H), 10.58 (s, 1 H).

Preparation 7b: 5-fluoro-2-methyl-3-[5-methyl-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester

[0080] A mixture of (5-fluor-2-methylindol-1-yl)acetic acid methyl ester (0.059 g), 5-methyl-3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde (0.071 g) and dichloroethane (1.5 mL) at 0°C was treated dropwise with a solution of triethylsilane (0.46 g) and trifluoroacetic acid (0.27 g) in dichloroethane (1.0 mL), and the resulting mixture was stirred at room temperature for 1 hour and then at 60°C for 1 hour. The mixture was cooled to room temperature and additional triethylsilane (2.7 g) and trifluoroacetic acid (1.6 g) were added, and the resulting mixture was stirred at room temperature for 1 hour. The mixture was partitioned between dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The phases were separated and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 2:3 by volume) to afford the title compound (0.060 g).
^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.26 (d, J = 1.1, 3H), 3.75 (s, 3H), 4.63 (s, 2H), 4.80 (s, 2H), 6.87 (dt, J = 2.5, 9.0, 1H), 6.95 (dd, J = 2.4, 9.5 Hz, 1H), 7.04-7.08 (m, 2H), 7.50-7.54 (m, 1H), 7.95 (dt, J = 1.7, 7.7 Hz, 1H), 8.19 (dt, J = 1.0, 7.9, Hz, 1H), 8.78-8.81 (m, 1H).
MS: ESI (+ve) (Method B): 473 $(M+H)^+$, Retention time 3.9 min.

Preparation 7c: {5-fluoro-2-methyl-3-[5-methyl-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl]acetic acid

[0081] The title compound was prepared by the method of Preparation E using 5-fluoro-2-methyl-3-[5-methyl-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid methyl ester.
^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H), 2.26 (d, J = 1.1 Hz, 3H), 4.50 (s, 2H), 4.95 (s, 2 H), 6.86 (dd, J = 2.5, 9.1 Hz, 1H), 6.90 (dd, J = 2.4, 10.1 Hz, 1H), 7.02 (d, J = 1.3 Hz, 1H), 7.35 (dd, J = 4.4, 8.8 Hz, 1 H), 7.76 (ddd, J = 1.3, 4.7, 7.5 Hz, 1H), 8.17 (td, J = 1.7, 7.6 Hz, 1H), 8.23 (dt, J = 1.1, 7.9 Hz, 1H), 8.79 (ddd, J = 0.9, 1.7, 4.7 Hz, 1H).
MS: ESI (+ve) (Method A): 459 $(M+H)^+$, Retention time 10.4 min.

Preparation F: 4-benzenesulfonylthiazole-5-carbaldehyde

[0082] A mixture of 4-chlorothiazole-5-carbaldehyde (0.15 g), benzenesulfinic acid sodium salt (0.25 g) and dimethyl sulfoxide (7.0 mL) was stirred at 100°C for 30 minutes. The mixture was cooled to room temperature, poured onto ice/water (50 mL) and extracted with ethyl acetate. The combined organic extract was washed with saturated aqueous sodium chloride solution and dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a tan oil (0.23 g).
^{1}H NMR ($CDCl_3$): δ 7.57-7.63 (m, 2H), 7.67-7.73 (m, 1H), 8.11-8.14 (m, 2H), 8.95 (d, J = 0.9 Hz, 1H), 10.83 (d, J = 0.9 Hz, 1H).

Preparation G: [3-(4-benzenesulfonylthiazol-5-ylmethyl)-5-fluoro-2-methylindol-1-yl]acetic acid methyl ester

[0083] A mixture of (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester (0.2 g), 4-benzenesulfonylthiazole-5-carbaldehyde (0.23 g) and 1,2-dichloroethane (7.0 mL) at 0°C was treated dropwise with a mixture of triethylsilane (2.2 mL), trifluoroacetic acid (0.6 mL) and 1,2-dichloroethane (2.0 mL), and the resulting mixture was stirred at room temperature overnight. The mixture was cooled to 0°C and diluted with saturated aqueous sodium hydrogen carbonate solution. The phases were separated and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue purified by column chromatography on silica gel, eluting with a mixture of ethyl acetate and dichloromethane (0:1 to 1:4 by volume) to afford the title compound as a white foam (0.20 g).
MS: ESI (+ve) (Method B): 459 $(M+H)^+$, Retention time 3.7 min.

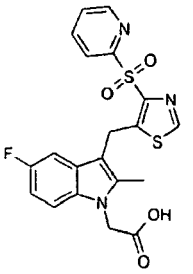
Preparation H: [3-(4-benzenesulfonylthiazol-5-ylmethyl)-5-fluoro-2-methylindol-1-yl]acetic acid

[0084] A mixture of lithium hydroxide (0.10 g), tetrahydrofuran (1.0 mL) and water (1.0 mL) was treated [3-(4-benzenesulfonylthiazol-5-ylmethyl)-5-fluoro-2-methylindol-1-yl]acetic acid methyl ester (0.20 g), and the resulting mixture was

stirred at room temperature for 30 minutes. The mixture was diluted with water, concentrated to low bulk under reduced pressure and acidified by the addition of 1.0 M aqueous hydrochloric acid solution. The resulting precipitate was collected by filtration, washed with water and dried to afford the title compound as a white solid (0.19 g).
^{1}H NMR (DMSO-d_6): δ 2.30 (s, 3H), 4.70 (s, 2H), 4.96 (s, 2H), 6.90 (td, J = 2.5, 9.2 Hz, 1H), 7.08 (dd, J = 2.5, 9.8 Hz, 1H), 7.39 (dd, J = 4.4, 8.9 Hz, 1H), 7.66-7.72 (m, 2H), 7.74-7.80 (m, 1H), 8.04-8.09 (m, 2H), 8.89 (s, 1H), 13.02 (br s, 1H).
MS: ESI (+ve) (Method A): 445 $(M+H)^+$, Retention time 10.1 min.
MS: ESI (+ve) (Method B): 445 $(M+H)^+$, Retention time 3.5 min.

Example 8: {5-fluoro-2-methyl-3-[4-(pyridine-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}acetic acid

[0085]



Preparation 8a: 4-(pyridine-2-sulfonyl)thiazole-5-carbaldehyde

[0086] The title compound was prepared by the method of Preparation F using 4-chlorothiazole-5-carbaldehyde and pyridine-2-sulfinate sodium salt.
^{1}H NMR ($CDCl_3$): δ 7.54-7.59 (m, 1H), 7.99-8.06 (m, 1H), 8.34-8.38 (m, 1H), 8.67-8.71 (m, 1H), 8.96 (d, J = 0.9 Hz, 1H), 10.85 (d, J = 0.8 Hz, 1H).

Preparation 8b: {5-fluoro-2-methyl-3-(4-(pyridine-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}acetic acid methyl ester

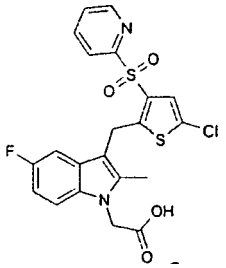
[0087] The title compound was prepared by the method of Preparation G using 4-(pyridine-2-sulfonyl)thiazole-5-carbaldehyde and (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester.
MS: ESI (+ve) (Method B): 460 $(M+H)^+$, Retention time 3.5 min.

Preparation 8c: {5-fluoro-2-methyl-3-[4-(pyridine-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}acetic acid

[0088] The title compound was prepared by the method of Preparation H using {5-fluoro-2-methyl-3-[4-(pyridine-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}acetic acid methyl ester.
^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H), 4.77 (s, 2H), 4.97 (s, 2H), 6.91 (td, J = 2.5, 9.2 Hz, 1H), 7.30 (dd, J = 2.5, 9.9 Hz, 1H), 7.39 (dd, J = 4.4, 8.9 Hz, 1H) 7.76-7.81 (m, 1H), 8.19-8.24 (m, 1H), 8.28 (dt, J = 1.1, 7.9 Hz, 1H), 8.75-8.78 (m, 1H), 8.87 (s, 1H), 12.98 (br s, 1H).
MS: ESI (+ve) (Method A): 446 $(M+H)^+$, Retention time 9.1 min.
MS: ESI (+ve) (Method B): 446 $(M+H)^+$, Retention time 3.3 min.

Example 9: {3-[5-chloro-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]-5-fluoro-2-methylindol-1-yl}acetic acid

[0089]



Preparation 9a: 5-chloro-3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde

[0090] The title compound was prepared by the method of Preparation F using 3,5-dichlorothiophene-2-carbaldehyde and pyridine-2-sulfinate sodium salt.
^{1}H NMR ($CDCl_3$): δ 7.53-7.5 (m, 1H), 7.76 (s, 1H), 7.99 (td, J = 1.7, 7.8 Hz, 1H), 8.17-8.22 (m, 1H), 8.73-8.76 (m, 1H), 10.08 (s, 1H).

Preparation 9b: {3-[5-chloro-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]-5-fluoro-2-methylindol-1-yl}acetic acid methyl ester

[0091] The title compound was prepared by the method of Preparation G using 5-chloro-3-(pyridine-2-sulfonyl)thiophene-2-carbaldehyde and (5-fluoro-2-methylindol-1-yl)acetic acid methyl ester.
MS: ES) (+ve) (Method B): 493 $(M+H)^+$, Retention time 4.0 min.

Preparation 9c: {3-[5-chloro-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]-5-fluoro-2-methylindol-1-yl}acetic acid

[0092] The title compound was prepared by the method of Preparation H using {3-[5-chloro-3-(pyridine-2-sulfonyl) thiophen-2-ylmethyl]-5-fluoro-2-methylindol-1-yl}acetic acid methyl ester.
^{1}H NMR (DMSO-d_6): δ 2.2 (s, 3H), 4.23 (s, 2H), 4.84 (s, 2H), 6.89 (td, J = 2.5, 9.2 Hz, 1H), 7.16 (dd, J = 2.5, 9.9 Hz, 1H), 7.36 (dd, J = 4.4, 8.9 Hz, 1H), 7.65-7.73 (m, 1H), 7.85 (s, 1H), 8.10-8.14 (m, 2H), 8.70 (dt, J = 1.3, 4.7 Hz, 1H).
MS: ESI (+ve) (Method A): 479 $(M+H)^+$, Retention time 11.1 min.
MS: ESI (+ve) (Method B): 479 $(M+H)^+$, Retention time 3.7 min.

Biological Methods

[0093] Compounds of the invention were tested using the following biological test method to determine their ability to displace PGD_2 from the CRTH2 receptor.

CRTH2 Radioligand Binding Assay

[0094] The receptor binding assay is performed in a final volume of 200 μL binding buffer [10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01% BSA] and 1 nM [^{3}H]-PGD_2 (Amersham Biosciences UK Ltd). Ligands are added in assay buffer containing a constant amount of DMSO (1% by volume). Total binding is determined using 1% by volume of DMSO in assay buffer and non-specific binding is determined using 10 μM of unlabeled PGD_2 (Sigma). Human embryonic kidney (HEK) cell membranes (3.5 μg) expressing the CRTH2 receptor are incubated with 1.5 mg wheatgerm agglutinin SPA beads and 1 nM [^{3}H]-PGD_2 (Amersham Biosciences UK Ltd) and the mixture incubated for 3 hours at room temperature. Bound [^{3}H]-PGD_2 is detected using a Microbeta TRILUX liquid scintillation counter (Perkin Elmer). Compound IC_{50} value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC_{50} calculations are performed using Excel and XLfit (Microsoft), and this value is used to determine a K_i value for the test compound using the Cheng-Prusoff equation.

GTPγS Functional Assay

[0095] The GTP□S Assay is performed in a final volume of 200 mL assay buffer (20 mM HEPES pH 7.4, 10 mM $MgCl_2$, 100 mM NaCl, 10 μg/mL saponin). DMSO concentrations are kept constant at 1% by volume. Human embryonic kidney (HEK) cell membranes (3.5 μg) expressing the CRTH2 receptor are incubated with the compounds for 15 min at 30°C prior to addition of PGD_2 (30 nM final concentration) and GTP (10 μM final concentration). The assay solutions are then incubated for 30 minutes at 30°C, followed by addition of [^{35}S]-GTPγS (0.1 nM final concentration). The assay

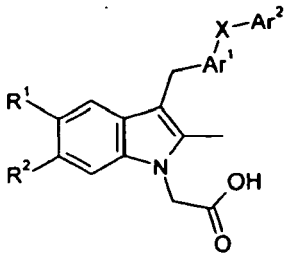
plate is than shaken and incubated for 5 minutes at 30°C. Finally, SPA beads (Amersham Biosciences, UK) are added to a final concentration of 1.5 mg/well and the plate shaken and incubated for 30 minute at 30°C. The sealed plate is centrifuged at 1000 g for 10mins at 30°C and the bound [^{35}S]-GTPγS is detected on Microbeta scintillation counter (Perkin Elmer). Compound IC_{50} value is determined using a 6-point dose response curve in duplicate with a semi-log compound dilution series. IC_{50} calculations are performed using Excel and XLfit (Microsoft), and this value is used to determine a Ki value for the test compound using the Cheng-Prusoff equation.

Biological Results

[0096] All compounds of the Examples above were tested in the CRTH2 radioligand binding assay described above; the compounds had a K_i value of less than 2 μM in the binding assay. For example, the compound of Example 2 had a K_i value of nM. That compound was tested in the GTPγS functional assay, and had a K_i value of less than 10 nM.

Claims

1. A compound that is an indole derivative of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein X is -SO_2- or *-SO_2NR^3- wherein the bond marked with an asterisk is attached to Ar^1;
R^1 is hydrogen, fluoro, chloro, CN or CF_3;
R^2 is hydrogen, fluoro or chloro;
R^3 is hydrogen, C_1-C_8alkyl or C_3-C_7cycloalkyl;
Ar^1 is a 5- or 6-membered heteroaryl group selected from furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from fluoro, chloro, CN, C_3-C_7cycloalkyl, -O(C_1-C_4alkyl) or C_1-C_6alkyl, the latter two groups being optionally substituted by one or more fluoro atoms; and
Ar^2 is a 5- or 6-membered heteroaryl group selected from pyrrolyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridinyl, pyridazinyl, pyrimidinyl and pyrazinyl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from fluoro, chloro, CN; C_3-C_7cycloalkyl, -O(C_1-C_4alkyl) or C_1-C_6alkyl, the latter two groups being optionally substituted by one or more fluoro atoms.

2. A compound as claimed in claim 1 wherein R^2 is hydrogen and R^1 is fluoro or chloro.

3. A compound as claimed in claim 1 or claim 2 wherein X is *-SO_2NR^3- wherein the bond marked with an asterisk is attached to Ar^1.

4. A compound as claimed in any of the preceding claims wherein the radical Ar^2SO_2- or $Ar^2N(R^3)SO_2$- is in the meta- or para-position of the ring Ar^1 relative to the point of attachment of Ar^1 to the rest of the molecule.

5. A compound as claimed in any of claims 1 to 3 wherein the radical Ar^2SO_2- or $Ar^2N(R^3)SO_2$- is in the ortho-position of the ring Ar^1 relative to the point of attachment of Ar^1 to the rest of the molecule.

6. A compound as claimed in any of the preceding claims wherein Ar^1 is selected from thienyl, pyridinyl, pyrimidinyl,

thiazolyl, isothiazolyl and imidazolyl.

7. A compound as claimed in any of the preceding claims wherein ring Ar^2 is selected from thienyl, pyridinyl, and pyrimidinyl.

8. A compound as claimed in any of the preceding claims wherein optional substituents in Ar^1 and Ar^2 are selected from chloro, fluoro, -CN and methyl.

9. A compound as claimed in claim 1, selected from

{5-fluoro-2-methyl-3-[3-(thiophene-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid
{5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}acetic acid
{5-fluoro-2-methyl-3-[3-(pyridine-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid
{5-chloro-2-methyl-3-[3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid
{5-fluoro-2-methyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylmethyl]indol-1-yl}acetic acid
{5-fluoro-2-methyl-3-[5-methyl-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}acetic acid
{5-fluoro-2-methyl-3-[4-(pyridine-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}acetic acid
{3-[5-chloro-3-(pyridine-2-sulfonyl)thiophen-2-ylmethyl]-5-fluoro-2-methylindol-1-yl}acetic acid

and pharmaceutically acceptable salts thereof.

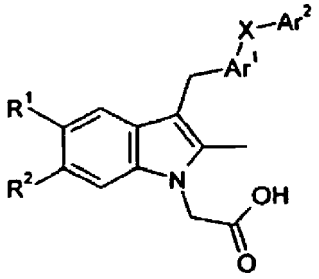
10. A pharmaceutical composition comprising a compound as claimed in any of the preceding claims and a pharmaceutically acceptable carrier.

11. A compound as claimed in any of claims 1 to 9, for use in the treatment of asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome, or allergic rhinobronchitis.

12. A compound as claimed in any of claims 1 to 9, for use in the treatment of psoriasis, atopic and non-atopic dermatitis, Crohn's disease, ulcerative colitis, or irritable bowel disease.

Patentansprüche

1. Verbindung, bei der es sich um ein Indolderivat der Formel (I) handelt, oder ein pharmazeutisch verträgliches Salz davon:



(I)

wobei X $-SO_2-$ oder $*-SO_2NR^3-$ ist, wobei die mit einem Sternchen versehene Bindung an Ar^1 angelagert ist;
R^1 Wasserstoff, Fluoro, Chloro, CN oder CF_3 ist;
R^2 Wasserstoff, Fluoro oder Chloro ist;
R^3 Wasserstoff, C_1-C_8-Alkyl oder C_3-C_7-Cycloalkyl ist;
Ar^1 eine 5- oder 6-gliedrige Heteroarylgruppe ist, ausgewählt aus Furanyl, Thienyl, Oxazolyl, Thiazolyl, Imidazolyl, Pyrazolyl, Isoxazolyl, Isothiazolyl, Pyridinyl, Pyridazinyl, Pyrimidinyl und Pyrazinyl, wobei die Phenyl- oder Heteroarylgruppen gegebenenfalls durch einen oder mehr Substituenten substituiert sind, der/die unabhängig ausgewählt ist/sind aus Fluoro, Chloro, CN, C_3-C_7-Cycloalkyl, $-O(C_1$-C_4-Akyl) oder C_1-C_6-Alkyl, wobei die letzteren beiden Gruppen gegebenenfalls durch ein oder mehr Fluoratom(e) substituiert sind; und

Ar^2 eine 5- oder 6-gliedrige Heteroarylgruppe ist, ausgewählt aus Pyrrolyl, Furanyl, Thienyl, Oxazolyl, Thiazolyl, Imidazolyl, Pyrazolyl, Isoxazolyl, Isothiazolyl, Pyridinyl, Pyridazinyl, Pyrimidinyl und Pyrazinyl, wobei die Phenyl- oder Heteroarylgruppen gegebenenfalls durch einen oder mehr Substituenten substitutiert sind, der/die unabhängig ausgewählt ist/sind aus Fluoro, Chloro, CN, C_3-C_7-Cycloalkyl, -O(C_1-C_4-Alkyl) oder C_1-C_6-Alkyl, wobei die beiden letzteren Gruppen gegebenenfalls durch ein oder mehr Fluoratom(e) substituiert sind.

2. Verbindung nach Anspruch 1, wobei R^2 Wasserstoff ist und R^1 Fluoro oder Chloro ist.

3. Verbindung nach Anspruch 1 oder 2, wobei X*-SO_2NR^3- ist, wobei die mit einem Sternchen versehene Bindung an Ar^1 angelagert ist.

4. Verbindung nach einem der vorangehenden Ansprüche, wobei sich der Rest Ar^2SO_2- oder $Ar^2N(R^3)SO_2$- in der meta- oder para-Position des Rings Ar^1 relativ zum Punkt der Anlagerung von Ar^1 an den Rest des Moleküls befindet.

5. Verbindung nach einem der Ansprüche 1 bis 3, wobei sich der Rest Ar^2SO_2- oder $Ar^2N(R^3)SO_2$- in der ortho-Position des Rings Ar^1 relativ zum Punkt der Anlagerung von Ar^1 an den Rest des Moleküls befindet.

6. Verbindung nach einem der vorangehenden Ansprüche, wobei Ar^1 ausgewählt ist aus Thienyl, Pyridinyl, Pyrimidinyl, Thiazolyl, Isothiazolyl und Imidazolyl.

7. Verbindung nach einem der vorangehenden Ansprüche, wobei Ring Ar^2 aus Thienyl, Pyridinyl und Pyrimidinyl ausgewählt ist.

8. Verbindung nach einem der vorangehenden Ansprüche, wobei gegebenenfalls Substituenten in Ar^1 und Ar^2 aus Chloro, Fluoro, -CN und Methyl ausgewählt sind.

9. Verbindung nach Anspruch 1, ausgewählt aus:

{5-Fluor-2-methyl-3-[3-(thiophen-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}essigsäure
{5-Fluor-3-[3-(pyridin-3-sulfonyl)thiophen-2-ylmethyl]-2-methylindol-1-yl}essigsäure
{5-Fluor-2-methyl-3-[3-(pyridin-4-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}essisäure
{5-Chlor-2-methyl-3-[3-(pyridin-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}essigsäure
{5-Fluor-2-methyl-3-[5-(pyridin-2-sulfonyl)thiazol-4-ylmethyl]indol-1-yl}essigsäure
{5-Fluor-2-methyl-3-[5-methyl-3-(pyridin-2-sulfonyl)thiophen-2-ylmethyl]indol-1-yl}essigsäure
{5-Fluor-2-methyl-3-[4-(pyridin-2-sulfonyl)thiazol-5-ylmethyl]indol-1-yl}essigsäure
{3-[5-Chlor-3-(pyridin-2-sulfonyl)thiophen-2-ylmethyl]-5-fluor-2-methylindol-1-yl}essigsäure

und pharmazeutisch verträgliche Salzen davon.

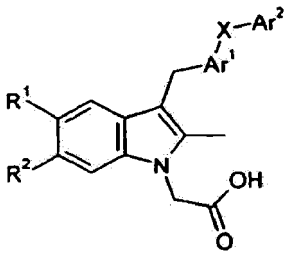
10. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach einem der vorangehenden Ansprüche und einen pharmazeutisch verträglichen Träger.

11. Verbindung nach einem der Ansprüche 1 bis 9, zur Verwendung in der Behandlung von Asthma, der chronisch obstruktiven Lungenerkrankung, Rhinitis, der allergischen Atemwegserkrankung oder allergischen Rhinobronchitis.

12. Verbindung nach einem der Ansprüche 1 bis 9, zur Verwendung in der Behandlung von Psoriasis, atopischer und nicht atopischer Dermatitis, Morbus Crohn, Colitis ulcerosa oder der Reizdarmerkrankung.

Revendications

1. Composé qui est un dérivé indole de la formule (I) ou un sel pharmaceutiquement acceptable de celui-ci :



(I)

où X est $-SO_2-$ ou $*-SO_2NR^3-$, où la liaison dénotée par un astérisque est attachée à Ar^1;
R^1 est hydrogène, fluoro, chloro, CN ou CF_3;
R^2 est hydrogène, fluoro ou chloro;
R^3 est hydrogène, alkyle C_1-C_8 ou cycloalkyle C_3-C_7;
Ar^1 est un groupe hétéroaryle à 5 ou 6 chaînons sélectionné parmi furanyle, thiényle, oxazolyle, thiazolyle, imidazolyle, pyrazolyle, isoxazolyle, isothiazolyle, pyridinyle, pyridazinyle, pyrimidinyle et pyrazinyle, où les groupes phényle ou hétéroaryle sont optionnellement substitués par un ou plusieurs substituants sélectionnés indépendamment parmi fluoro, chloro, CN, cycloalkyle C_3-C_7, -O(alkyle C_1-C_4) ou alkyle C_1-C_6, les deux derniers groupes étant optionnellement substitués par un ou plusieurs atomes de fluor; et
Ar^2 est un groupe hétéroaryle à 5 ou 6 chaînons sélectionné parmi pyrrolyle, furanyle, thiényle, oxazolyle, thiazolyle, imidazolyle, pyrazolyle, isoxazolyle, isothiazolyle, pyridinyle, pyridazinyle, pyrimidinyle et pyrazinyle, où les groupes phényle ou hétéroaryle sont optionnellement substitués par un ou plusieurs substituants sélectionnés indépendamment parmi fluoro, chloro, CN, cycloalkyle C_3-C_7, -O(alkyle C_1-C_4) ou alkyle C_1-C_6, les deux derniers groupes étant optionnellement substitués par un ou plusieurs atomes de fluor.

2. Composé selon la revendication 1, dans lequel R^2 est hydrogène et R^1 est fluoro ou chloro.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel X est $*-SO_2NR^3-$, où la liaison dénotée par un astérisque est attachée à Ar^1.

4. Composé selon l'une quelconque des revendications précédentes, dans lequel le radical Ar^2SO_2- ou $Ar^2N(R^3)SO_2-$ est en position méta ou para du cycle Ar^1 par rapport au point d'attache de Ar^1 au reste de la molécule.

5. Composé selon l'une quelconque des revendications 1 à 3, dans lequel le radical Ar^2SO_2- ou $Ar^2N(R^3)SO_2-$ est en position ortho du cycle Ar^1 par rapport au point d'attache de Ar^1 au reste de la molécule.

6. Composé selon l'une quelconque des revendications précédentes, dans lequel Ar^1 est sélectionné parmi thiényle, pyridinyle, pyrimidinyle, thiazolyle, isothiazolyle et imidazolyle.

7. Composé selon l'une quelconque des revendications précédentes, dans lequel le cycle Ar^2 est sélectionné parmi thiényle, pyridinyle et pyrimidinyle.

8. Composé selon l'une quelconque des revendications précédentes, dans lequel les substituants optionnels dans Ar^1 et Ar^2 sont sélectionnés parmi chloro, fluoro, -CN et méthyle.

9. Composé selon la revendication 1, sélectionné parmi :

acide {5-fluoro-2-méthyl-3-[3-(thiophène-2-sulfonyl)thiophén-2-ylméthyl]indol-1-yl}acétique,
acide {5-fluoro-3-[3-(pyridine-3-sulfonyl)thiophén-2-ylméthyl]-2-méthylindol-1-yl}acétique,
acide {5-fluoro-2-méthyl-3-[3-(pyridine-4-sulfonyl)thiophén-2-ylméthyl]indol-1-yl}acétique,
acide {5-chloro-2-méthyl-3-[3-(pyridine-2-sulfonyl)thiophén-2-ylméthyl]indol-1-yl}acétique,
acide {5-fluoro-2-méthyl-3-[5-(pyridine-2-sulfonyl)thiazol-4-ylméthyl]indol-1-yl}acétique,
acide {5-fluoro-2-méthyl-3-[5-méthyl-3-(pyridine-2-sulfonyl)thiophén-2-ylméthyl]indol-1-yl}acétique,
acide {5-fluoro-2-méthyl-3-[4-(pyridine-2-sulfonyl)thiazol-5-ylméthyl]indol-1-yl}acétique,
acide {5-chloro-3-(pyridine-2-sulfonyl)thiophén-2-ylméthyl]-5-fluoro-2-méthylindol-1-yl}acétique,

et des sels pharmaceutiquement acceptables de ceux-ci.

10. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications précédentes et un véhicule pharmaceutiquement acceptable.

11. Composé selon l'une quelconque des revendications 1 à 9, à utiliser dans le traitement de l'asthme, d'une maladie pulmonaire obstructive chronique, de la rhinite, d'un syndrome allergique des voies aériennes ou d'une rhino-bronchite allergique.

12. Composés selon l'une quelconque des revendications 1 à 9, à utiliser dans le traitement du psoriasis, de la dermatite atopique et non atopique, de la maladie de Crohn, de colite ulcéreuse ou du syndrome de l'intestin irritable.

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