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(54) Title: 6,6-FUSED BICYCLIC AROMATIC COMPOUNDS AND THEIR THERAPEUTI USE

(57) Abstract: This invention relates to a class of 6,6-fused bicyclic aromatic 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 sgnificant inflammatory component. the invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

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6,6-FUSED BICYCLIC AROMATIC COMPOUNDS AND THEIR THERAPEUTIC USE

Field of the Invention

This invention relates to a class of 6,6-fused bicyclic aromatic compounds which are ligands of the CRTH2 receptor (Chemoattractant Receptor-homologous molecule expressed on T Helper cells type 2), and their use in the treatment of diseases responsive to modulation of CRTH2 receptor activity, principally diseases having a significant inflammatory component. The invention also relates to novel members of that class of ligands and pharmaceutical compositions containing them.

Background to the Invention

Mast cells are known to play an important role in allergic and immune responses through the release of a number of mediators, such as histamine, leukotrienes, cytokines, prostaglandin D_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 cells (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 number of disease states.

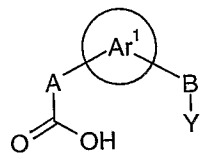
The CRTH2 receptor has been shown to be expressed on cell types associated with allergic inflammation, such as basophils, eosinophils, and Th2-type immune helper cells (Hirai et al; J. Exp. Med., 2001, 193, 255-261). The CRTH2 receptor has been shown to mediate PGD_2-mediated cell migration in these 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)sulphonyl-

amino]-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.

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; WO2003/097598; 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).

Detailed Description of the Invention

One aspect of the invention provides compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

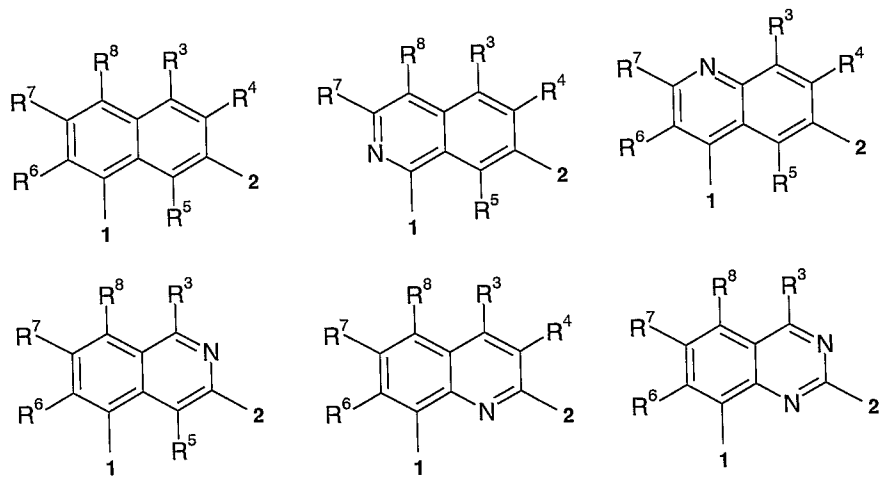
wherein:

A is selected from $-CR^1R^2-$, $-CR^1R^2CR^1R^2-$ or $-D(CR^1R^2)-$, wherein D is O, NR^1 or $S(O)_n$, and is attached to the Ar^1 ring;

R^1 and R^2 independently represent hydrogen or C_1-C_3alkyl;

B is $-CH_2-$, $-S(O)_n-$, or -O-;

Ar^1 is selected from one of the following formulae, wherein the bond marked 1 is attached to A while the bond marked 2 is attached to B;



R^3, R^4, R^5, R^6, R^7 and R^8 independently represent hydrogen, halogen, -CN, $-OR^9$, $-NR^{10}R^{11}$, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms;

R^9 is C_1-C_6alkyl or C_3-C_7cycloalkyl, optionally substituted by one or more fluoro atoms;

R^{10} and R^{11} independently represent hydrogen, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms;

Y is phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from halogen, -CN, $-S(O)_nR^9$, $-S(O)_2NR^{12}R^{13}$, $-NR^{12}S(O)_2R^9$ $-NR^{12}R^{13}$, $-NR^{12}COR^9$, $-CONR^{12}R^{13}$, $-COR^9$, $-OR^9$, C_1-C_6alkyl, C_3-C_7cycloalkyl, phenyl and 5- or 6-membered heteroaryl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms and the phenyl and 5- or 6-membered heteroaryl substituents are optionally substituted with one or more substituents independently selected from halogen, CN, C_1-C_6alkyl, C_3-C_7cycloalkyl, $-O(C_1$-C_6alkyl) or $-O(C_3$-C_7cycloalkyl), and wherein the alkyl substituents and alkyl part of the $-O(C_1$-C_6alkyl) substituent are optionally substituted with one or more fluoro atoms;

R^{12} and R^{13} independently represent hydrogen, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituent is optionally substituted with one or more fluoro atoms; or R^{12} and R^{13} when attached to the same atom may form a 3-8 membered ring optionally containing one or more ring components selected from -O-, $-S(O)_n$- or $-NR^{14}$-, and optionally substituted with one or more fluoro or C_1-C_3 alkyl substituents;

R^{14} is hydrogen, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $S(O)_2R^{15}$ or COR^{15};

R^{15} is C_1-C_6alkyl or C_3-C_7cycloalkyl; and

n is 0, 1 or 2.

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 DP receptor or the thromboxane A_2 receptor.

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

The invention also includes (i) use of a compound with which the invention is concerned in the manufacture of a medicament for use in the treatment of conditions

responsive to modulation of CRTH2 receptor activity, and (ii) a method of treatment of conditions responsive to modulation of CRTH2 receptor activity, comprising administering to a patient suffering such disease an effective amount of a compound with which the invention is concerned.

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

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

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

Terminology

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

As used herein the term "cycloalkyl" refers to a monocyclic saturated carbocyclic radical having from 3-6 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the unqualified term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical, and includes radicals having two monocyclic carbocyclic aromatic rings which are directly linked by a covalent bond. Aryl radicals may have, for example, from 6 to 14 ring carbon atoms, preferably from 6 to 10 carbon atoms. Illustrative of aryl radicals are phenyl, biphenyl and napthyl.

As used herein the unqualified term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O, and includes radicals having two such monocyclic rings, or one such monocyclic ring and one monocyclic aryl ring, which are directly linked by a covalent bond. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyridazinyl, triazinyl, indolyl and indazolyl.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically acceptable salts, with bases such as alkali metal hydroxides, for example sodium and potassium hydroxides; alkaline earth metal hydroxides, for example calcium, barium and magnesium hydroxides; with organic bases, for example *N*-methyl-D-glucamine, choline tris(hydroxymethyl)amino-methane, L-arginine, L-lysine, *N*-ethyl piperidine, dibenzylamine and the like. Specific salts with bases include the benzathine, calcium, diolamine, meglumine, olamine, potassium, procaine, sodium, tromethamine and zinc salts. Those compounds of the invention which are basic can form salts, including pharmaceutically acceptable salts with inorganic acids, for example with hydrohalic acids such as hydrochloric or

hydrobromic acids, sulphuric acid, nitric acid or phosphoric acid and the like, and with organic acids, for example acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic, *p*-toluenesulphonic, benzoic, 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.

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

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

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

Use of prodrugs, such as esters, of compounds with which the invention is concerned is also part of the invention. "Prodrug" means a compound which is convertible *in vivo* by metabolic means (for example, by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates,

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

In the compounds with which the invention is concerned, separately or in combination:

A may be $-OCH_2-$ or $-OCH(CH_3)-$ wherein the oxygen is attached to the Ar^1 ring system.

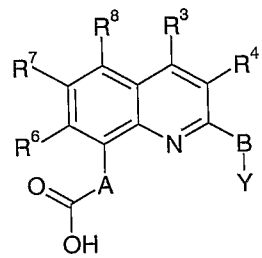
B may be $-CH_2-$.

Y may be phenyl, optionally substituted as specified above; or Y may be a monocyclic 5- or 6-membered heteroaryl group, such as thiophene or pyridine, optionally substituted as specified above. Examples of optional substituents in Y include chloro, fluoro, bromo, -CN, methyl, ethyl, isopropyl, cyclopropyl, trifluoromethyl, methoxy, isopropoxy, cyclopropoxy, difluoromethoxy, trifluoromethoxy, methanesulfonyl, ethanesulfonyl or pyrazole. Currently preferred substituents are chloro and pyrazolyl.

R^3, R^4 and R^5 may independently be hydrogen, C_1-C_3alkyl such as methyl, ethyl or isopropyl or a C_3-C_6cycloalkyl group such as cyclopropyl.

R^6, R^7 and R^8 may independently be hydrogen, C_1-C_3alkyl such as methyl, chloro, fluoro, bromo or trifluoromethyl.

One specific sub-class of compounds of the invention has the formula:



wherein A is $-OCH_2-$ or $-OCH(CH_3)-$ wherein the oxygen is attached to the ring carbon shown; B is $-CH_2-$, Y is as defined in relation to formula (I) above; R^3 and R^4 are independently selected from hydrogen, methyl, ethyl, isopropyl and cyclopropyl; and R^6, R^7 and R^8 are independently selected from hydrogen, methyl, chloro, fluoro, bromo and trifluoromethyl. Currently preferred is the case where Y is phenyl, substituted by choro or pyrazolyl.

Specific compounds with which the invention is concerned include those of the Examples herein.

Compositions

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

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

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. Orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium

phosphate, sorbitol or glycine; 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.

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

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

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

Other compounds may be combined with compounds with which the invention is concerned for the prevention and treatment of 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.

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

Synthesis

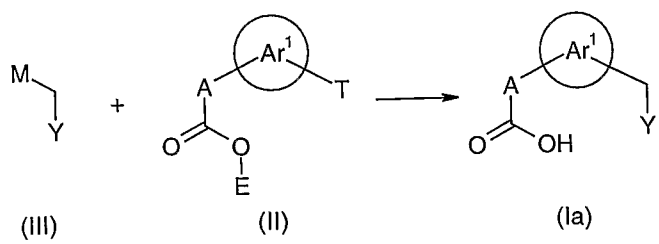
There are multiple synthetic strategies for the synthesis of the compounds with which the present invention is concerned, but all rely on known chemistry, known to the synthetic organic chemist. Thus, compounds of the invention can be synthesised according to procedures described in the standard literature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

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

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

Compounds of formula (I), wherein B is a $-CH_2-$ group are represented by compounds of formula (Ia) (Scheme 1). Compounds of the invention of formula (Ia) may be prepared from compounds of formula (II), wherein T is chloro, bromo, or iodo atom, or a trifluoromethanesulfonyloxy group and E is a hydrogen or alkyl group, by reaction with an organometallic reagent of formula (III), wherein M is an appropriately substituted boron, zinc or tin group. The reaction may conveniently be carried out in the presence of a suitable catalyst such as tetrakis(triphenylphosphine)palladium. Compounds of formula (III) are commercially available or can be prepared by known methods.

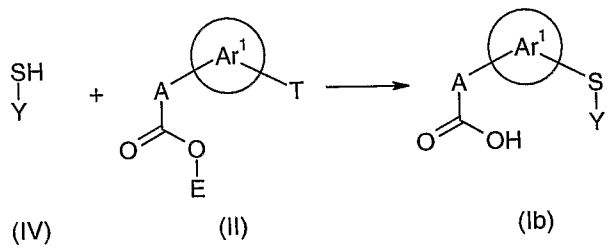


(III) (II) (Ia)

Scheme 1

It will be understood by those who are practiced in the art that it may be convenient to carry out the transformation of intermediates (II) and (III) to final compound (Ia), wherein one or other of the functionalities on either component is suitably protected. For example, it may be convenient to carry out the reaction using a form of (II), wherein the carboxylic acid group is protected as an ester (for example, an ethyl or *tert*-butyl ester). It is to be understood that if the reaction is carried out on a protected form of (II) an appropriate ester deprotection step will be required to obtain the desired compound of the invention of formula (Ia).

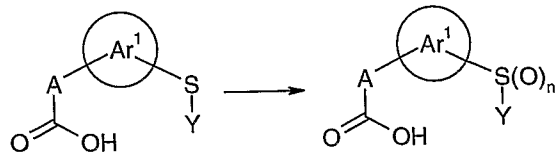
Compounds of the invention of formula (Ib), wherein B represents a -S- group, may be prepared by the reaction between a compound of formula (II) and a thiol of formula (IV) (Scheme 2). The reaction may be carried out in the presence of a suitable catalyst such as tetrakis(triphenylphosphine)palladium or tris(dibenzylideneacetone)dipalladium / 9,9-dimethyl-4,5-bis(diphenylphosphino xanthene. Compounds of formula (IV) are commercially available or can be prepared by known methods. It is to be understood that if the reaction is carried out on a protected form of (II) an appropriate ester deprotection step will be required to obtain the desired compound of the invention of formula (Ib).



(IV) (II) (Ib)

Scheme 2

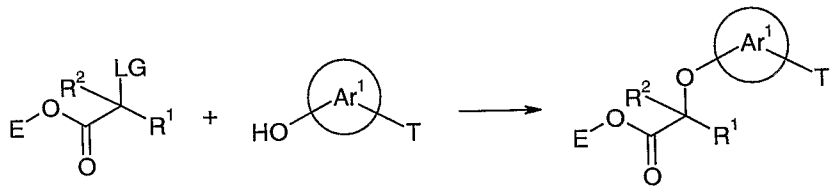
Compounds of the invention of formula (Ic), wherein B represents a -S(O)- or -$S(O)_2$- group, may be prepared by the oxidation of compounds of the invention of formula (Ib), with a suitable oxidising agent such as potassium peroxymonosulfate, *meta*-chloroperoxybenzoic acid or other well known oxidising agents (Scheme 3).



(Ib) (Ic) n = 1 or 2

Scheme 3

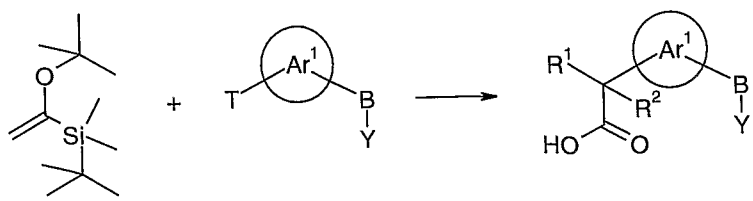
Intermediate compounds of formula (II), wherein A is a $-O(CR^1R^2)-$ group, may be prepared from compounds of formula of (V) by reaction with a suitable alkylating agent of formula (VI), wherein LG group represents a suitable leaving group such as chloro, bromo or methanesulfonyloxy group (Scheme 4). Typically, the alkylation reaction is carried out in the presence of a suitable base (for example, potassium carbonate) and solvent (for example, acetone or *N,N*-dimethylformamide). Compounds of formula (V) and (VI) are commercially available or can be prepared by known methods.



(VI) (V) (II)

Scheme 4

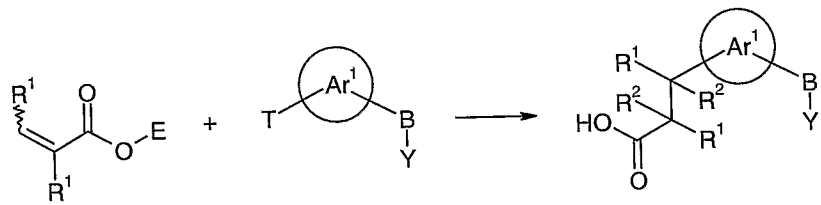
Compounds of formula (I), wherein A is a $-CR^1R^2-$ group are represented by compounds of formula (Id) (Scheme 5). Compounds of the invention of formula (Id) may be prepared by the reaction between a compound of formula (VII) and (1-*tert*-butoxyvinyloxy)-*tert*-butyldimethylsilane, followed by an appropriate ester deprotection step. The reaction may carried out in the presence of a suitable catalyst (for example, tetrakis(triphenylphosphine)palladium) and base (for example, lithium acetate).



(VII) (Id) R^1 and R^2 = H

Scheme 5

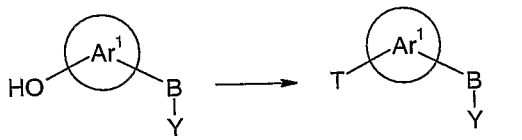
Similarly, compounds of the invention of formula (Ie), wherein A represents a $-CR^1R^2CR^1R^2-$ group, may be prepared by the reaction between a compound of formula (VII) and a compound of formula (VIII), followed by reduction with hydrogen in the presence of a suitable catalyst (for example, palladium supported on carbon) (Scheme 6). It is to be understood that if the reaction is carried out on a protected form of intermediate (VIII) an appropriate ester deprotection step will be required to obtain the desired compound of the invention of formula (Ie). Compounds of formula (VIII) are commercially available or can be prepared by known methods.



(VIII) (VII) (Ie) $R^2 = H$

Scheme 6

Intermediate compounds of formula (VII), wherein T represents trifluoromethanesulfonyloxy group, may be prepared from the reaction of compounds of formula (IX) with triflic anhydride in the presence of a suitable base (for example, 2,6-lutidine) (Scheme 7).



(IX) (VII) $T = OS(O)_2CF_3$

Scheme 7

Compounds of formula (IX) can be prepared from compounds of formula (V) using the methods describe above for the synthesis of compounds of formula (Ia) and (Ib) from compounds of formula (II) (Scheme 1 and 2) and compounds of formula (Ic) from compounds of formula (Ib) (Scheme 3).

Examples

^1H NMR spectra were recorded at ambient temperature using a Varian Unity Inova (400MHz) spectrometer with a triple resonance 5 mm probe spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. The following abbreviations

have been used: br s = broad singlet, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet.

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

Method A: experiments were performed on a Micromass Platform LCT spectrometer with positive ion electrospray and single wavelength UV 254 nm detection using a Higgins Clipeus C18 5 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.

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

Method C: Agilent Scalar column C18, 5 µm (4.6 x 50 mm, flow rate 2.5 mL / min) eluting with a H_2O-MeCN gradient containing 0.1% v/v formic acid over 7 minutes with UV detection at 215 and 254 nm. Gradient information: 0.0 – 0.1 min: 95% H_2O-5% MeCN; 0.1 -5.0 min; Ramp from 95% H_2O-5% MeCN to 5% H_2O-95% MeCN; 5.0 – 5.5 min: Hold at 5% H_2O-95% MeCN; 5.5 – 5.6 min: Hold at 5% H_2O-95% MeCN, flow rate increased to 3.5 mL/min; 5.6 – 6.6 min: Hold at 5% H_2O-95% MeCN, flow rate 3.5 mL/min; 6.6 – 6.75 min: Return to 95% H_2O-5% MeCN, flow rate 3.5 mL/min; 6.75 – 6.9 min: Hold at 95% H_2O-5% MeCN, flow rate 3.5 mL/min; 6.9 – 7.0 min: Hold at 95% H_2O-5% MeCN, flow rate reduced to 2.5 mL/min Mass spectra were obtained using an electrospray ionization source in either the positive (ESI^+) or negative (ESI^-) mode.

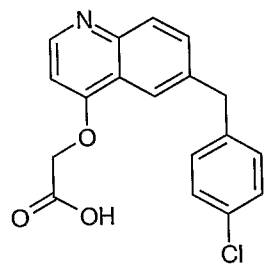
Method D: Agilent Scalar column C18, 5 µm (4.6 x 50 mm, flow rate 2.5 mL/min) eluting with a H_2O-MeCN gradient containing 0.1% v/v NH_4OH over 7 minutes with UV detection at 215 and 254 nm. Gradient information: 0.0 – 0.1 min: 95% H_2O-5% MeCN; 0.1 -5.0 min; Ramp from 95% H_2O-5% MeCN to 5% H_2O-95% MeCN; 5.0 –

5.5 min: Hold at 5% H_2O-95% MeCN; 5.5 – 5.6 min: Hold at 5% H_2O-95% MeCN, flow rate increased to 3.5 mL/min; 5.6 – 6.6 min: Hold at 5% H_2O-95% MeCN, flow rate 3.5 mL/min; 6.6 – 6.75 min: Return to 95% H_2O-5% MeCN, flow rate 3.5 mL/min; 6.75 – 6.9 min: Hold at 95% H_2O-5% MeCN, flow rate 3.5 mL/min; 6.9 – 7.0 min: Hold at 95% H_2O-5% MeCN, flow rate reduced to 2.5 mL/min Mass spectra were obtained using an electrospray ionization source in either the positive (ESI^+) or negative (ESI^-) mode.

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 bar can be reached. Two types of vial are available for this processor, 0.5-2.0 mL and 2.0-5.0 mL.

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, acetic acid or formic acid) with a flow rate of 5-20 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 LC-MS analysis) were pooled, the organic fraction removed by evaporation, and the remaining aqueous fraction lyophilised, to give the final product.

Example 1: [6-(4-chlorobenzyl)quinolin-4-yloxy]acetic acid



Preparation 1a: (6-bromoquinolin-4-yloxy)acetic acid methyl ester

A mixture of 6-bromo-1H-quinolin-4-one (0.50 g), *N,N*-dimethylformamide (10 mL) and potassium carbonate (0.34 g) was treated with methyl bromoacetate (0.21 mL), and the resulting mixture was stirred at 60 °C for 3 hours. The mixture was

concentrated under reduced pressure and the residue partitioned between dichloromethane and water. The organic phase was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate to afford the title compound as a yellow solid (0.053 g).

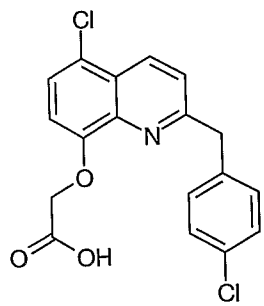
MS: ESI (+ve) (Method B): 297 $(M+H)^+$, Retention time 2.1 min.

Preparation 1b: [6-(4-chlorobenzyl)quinolin-4-yloxy]acetic acid

A mixture of (6-bromoquinolin-4-yloxy)acetic acid methyl ester (0.050 g), 0.5 M solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (0.85 mL), dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) (0.007 g) and tetrahydrofuran (1.0 mL) was heated at 60 °C overnight. The mixture was cooled to room temperature, diluted with tetrahydrofuran (3.0 mL) and water (1.0 mL) and then basified by the addition of 1.0 M aqueous sodium hydroxide solution. The resulting mixture was stirred at room temperature for 3 hours and concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford the title compound as a white solid (0.015 g).

^{1}H NMR (DMSO-d6): δ 4.16 (s, 2H), 5.09 (s, 2H), 7.12 (d, J = 5.7 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.72 (dd, J = 1.0, 8.6 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 1.0 Hz, 1H), 8.80 (d, J = 5.7 Hz, 1H), 13.30 (br s, 1H).
MS: ESI (+ve) (Method A): 328 $(M+H)^+$, Retention time 7.0 min.
MS: ESI (+ve) (Method B): 328 $(M+H)^+$, Retention time 2.4 min.

Example 2: [5-chloro-2-(4-chlorobenzyl)quinolin-8-yloxy]acetic acid



Preparation 2a: 2,5-dichloroquinolin-8-ol

A mixture of 2-chloroquinolin-8-ol (3.1 g) and sulfuric acid (120 mL) was treated with *N*-chlorosuccinimide (2.3 g), and the resulting mixture was stirred at room temperature overnight. The mixture was poured onto ice (600 g), extracted with ethyl acetate and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to afford the title compound as a pale yellow solid (3.8 g).

MS: ESI (+ve) (Method C): 214 $(M+H)^+$, Retention time 3.5 min.

Preparation 2b: (2,5-dichloroquinolin-8-yloxy)acetic acid methyl ester

A mixture of 2,5-dichloroquinolin-8-ol (0.19 g), *N,N*-dimethylformamide (1.0 mL) and potassium carbonate (0.15 g) was treated with methyl bromoacetate (0.079 mL), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was diluted with water and the resulting precipitate was collected by filtration. Purification of the precipitate by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:0 to 9:1 by volume) gave the title compound (0.13 g).

MS: ESI (+ve) (Method C): 286 $(M+H)^+$, Retention time 3.3 min.

Preparation 2c: [5-chloro-2-(4-chlorobenzyl)quinolin-8-yloxy]acetic acid methyl ester

A mixture of (2,5-dichloroquinolin-8-yloxy)acetic acid methyl ester (0.11 g), 0.5 M solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (0.88 mL), tetrakis(triphenylphosphine)palladium (0.008 g) and tetrahydrofuran (2.5 mL) was heated at 100 °C under microwave irradiation for 20 minutes. The mixture was diluted with water, extracted with ethyl acetate and the combined extracts were washed with 2.0 M aqueous acetic acid solution and saturated aqueous sodium hydrogen carbonate solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with a mixture of petroleum ether and ethyl acetate (5:1 by volume) to afford the title compound as a white solid (0.079 g).

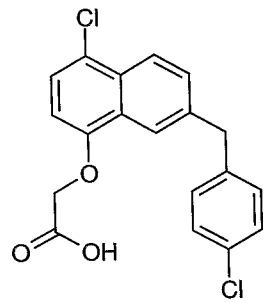
^{1}H NMR (DMSO-d6): δ 3.67 (s, 3H), 4.29 (s, 2H), 5.04 (s, 2H), 7.09 (d, J = 8.5 Hz, 1H), 7.29-7.34 (m, 4H), 7.53-7.58 (m, 2H), 8.40 (d, J = 8.7 Hz, 1H).

Preparation 2d: [5-chloro-2-(4-chlorobenzyl)quinolin-8-yloxy]acetic acid

A mixture of [5-chloro-2-(4-chlorobenzyl)quinolin-8-yloxy]acetic acid methyl ester (0.74 g), tetrahydrofuran (2.0 mL), 1.0 M aqueous lithium hydroxide solution (0.59 mL) and water (1.0 mL) was stirred at room temperature for 1 hour. The mixture was diluted with water and washed with diethyl ether. The aqueous phase was acidified by the addition of glacial acetic acid (1.0 mL) and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was triturated with diethyl ether to afford the title compound as a while solid (0.063 g).

^{1}H NMR (DMSO-d6): δ 4.28 (s, 2H), 4.91 (s, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.28-7.33 (m, 4H), 7.53 (d, J = 8.7 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 8.38 (d, J = 8.7 Hz, 1H), 13.05 (br s, 1H).
MS: ESI (+ve) (Method A): 362 $(M+H)^+$, Retention time 11.1 min.

Example 3: [4-chloro-7-(4-chlorobenzyl)naphthalen-1-yloxy]acetic acid



Preparation 3a: (7-bromonaphthalen-1-yloxy)acetic acid methyl ester

A mixture of 7-bromonaphthalen-1-ol (0.10 g), *N,N*-dimethylformamide (2.0 mL) and potassium carbonate (0.081 g) was treated with methyl bromoacetate (0.048 mL), and the resulting mixture was stirred at room temperature for 1 hour. The mixture was diluted with water, extracted with diethyl ether and the combined extracts were washed with a saturated aqueous sodium hydrogen carbonate solution and water and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting

with a mixture of petroleum ether and dichloromethane (5:1 by volume) to afford the title compound as a colourless oil (0.10 g).

^{1}H NMR (DMSO-d6): δ 3.69 (s, 3H), 5.00 (s, 2H), 6.97 (d, J = 7.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.63 (dd, J = 2.1, 8.7 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1H), 8.29 (d, J = 2.1 Hz, 1H).

Preparation 3b: (7-bromo-4-chloronaphthalen-1-yloxy)acetic acid methyl ester

A mixture of *N*-chlorosuccinimide (0.049 g), zirconium tetrachloride (0.004 g) and dichloromethane was treated with a solution of (7-bromonaphthalen-1-yloxy)acetic acid methyl ester (0.10 g) in dichloromethane (1.0 mL), and the resulting mixture was stirred at room temperature for 23 hours. The mixture was diluted with diethyl ether, washed with a saturated aqueous sodium hydrogen carbonate solution and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with a mixture of petroleum ether and dichloromethane (5:1 to 4:1 by volume) to afford the title compound (0.059 g).

^{1}H NMR (DMSO-d6): δ 3.69 (s, 3H), 5.01 (s, 2H), 7.00 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 2.1, 9.0 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 2.1 Hz, 1H).

Preparation 3c: [4-chloro-7-(4-chlorobenzyl)naphthalen-1-yloxy]acetic acid methyl ester

A mixture of (7-bromo-4-chloronaphthalen-1-yloxy)acetic acid methyl ester (0.20 g), 0.5 M solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (1.4 mL), tetrakis(triphenylphosphine)palladium (0.012 g) and tetrahydrofuran (2.5 mL) was heated at 100 °C under microwave irradiation for 5 minutes. The mixture was diluted with diethyl ether, filtered through hyflo and the filtrated concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of petroleum ether and dichloromethane (10:1 to 4:1 by volume), and then by flash chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (49:1 by volume) to afford the title compound (0.070 g).

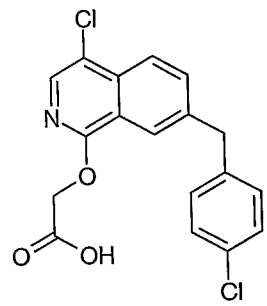
^{1}H NMR (DMSO-d6): δ 3.68 (s, 3H), 4.14 (s, 2H), 4.98 (s, 2H), 6.85 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 1.7, 8.7 Hz, 1H), 8.01 (d, J = 8.7 Hz, 1H), 8.07 (m, 1H).

Preparation 3d: [4-chloro-7-(4-chlorobenzyl)naphthalen-1-yloxy]acetic acid

A mixture of [4-chloro-7-(4-chlorobenzyl)naphthalen-1-yloxy]acetic acid methyl ester (0.10 g), tetrahydrofuran (2.0 mL), lithium hydroxide (0.013 g) and water (0.5 mL) was stirred at room temperature for 1 hour. The mixture was acidified by the addition of 2.0 M aqueous hydrochloric acid solution, extracted with ethyl acetate and the combined extracts were concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford the title compound as a white solid (0.059 g).

^{1}H NMR (DMSO-d6): δ 4.12 (s, 2H), 4.84 (s, 2H), 6.80 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 1.2, 8.7 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 1.2 Hz, 1H), 13.13 (br s, 1H).
MS: ESI (+ve) (Method A): 359 $(M-H)^-$, Retention time 13.0 min.

Example 4: [4-chloro-7-(4-chlorobenzyl)isoquinolin-1-yloxy]acetic acid



Preparation 4a: 7-bromo-4-chloro-2H-isoquinolin-1-one

A mixture of *N*-chlorosuccinimide (3.1 g), 7-bromo-2H-isoquinolin-1-one (4.3 g) and acetonitrile (20 mL) was heated at 90 °C for 5 hours. The mixture was cooled to room temperature, and the resulting precipitate was collected by filtration, washed with methanol and dried to afford the title compound as a pale brown solid (4.0g).

MS: ESI (+ve) (Method C): 258 $(M+H)^+$ Retention time 3.0 min.

Preparation 4b: 7-bromo-1,4-dichloroisoquinoline

A mixture of 7-bromo-4-chloro-2H-isoquinolin-1-one (1.0 g) and phosphorus oxychloride (3.0 mL) was heated at 100 °C for 3 hours. The mixture was cooled to room temperature, poured onto a mixture of ice and water, and the resulting precipitate was collected by filtration and dried to afford the title compound as an off white solid (0.82 g).

MS: ESI (+ve) (Method D): 277 $(M+H)^+$, Retention time 4.8 min.

Preparation 4c: (7-bromo-4-chloroisoquinolin-1-yloxy)acetic acid ethyl ester

A solution of ethyl glycolate (0.68 mL) in tetrahydrofuran (10 mL) was treated with sodium hydride (0.26 g), and the resulting mixture was stirred at room temperature for 45 minutes and then treated with a solution of 7-bromo-1,4-dichloroisoquinoline (1.0 g) in tetrahydrofuran (10 mL). The resulting mixture was stirred at room temperature for 30 minutes and then at 70 °C for 20 minutes in a sealed tube. The mixture was poured onto a saturated aqueous sodium chloride solution (75 mL), extracted with ethyl acetate and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified flash chromatography on silica gel, eluting with a mixture of hexane and dichloromethane (2:1 by volume) to afford the title compound as a colourless solid (1.0 g).

MS: ESI (+ve) (Method C): 345 $(M+H)^+$, Retention time 5.1 min.

Preparation 4d: [4-chloro-7-(4-chlorobenzyl)isoquinolin-1-yloxy]acetic acid ethyl ester

A mixture of (7-bromo-4-chloroisoquinolin-1-yloxy)acetic acid ethyl ester (0.40 g), 0.5 M solution of 4-chlorobenzylzinc chloride in tetrahydrofuran (5.8 mL), (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) (0.01 g) and tetrahydrofuran (8.0 mL) was heated at 100 °C under microwave irradiation for 10 minutes. The mixture was diluted with water, extracted with ethyl acetate and the combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with a mixture of hexane and dichloromethane (2:3 by volume) to afford the title compound (0.4 g).

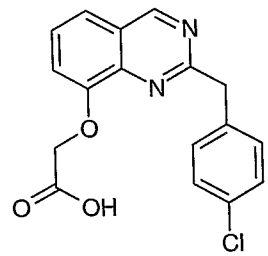
MS: ESI (+ve) (Method C): 390 $(M+H)^+$, Retention time 5.4 min.

Preparation 4e: [4-chloro-7-(4-chlorobenzyl)isoquinolin-1-yloxy]acetic acid

A solution of [4-chloro-7-(4-chlorobenzyl)isoquinolin-1-yloxy]acetic acid ethyl ester (0.35 g) in tetrahydrofuran (5.0 mL) and methanol (5.0 mL) was treated with a solution of lithium hydroxide (0.11 g) in water (0.5 mL), and the resulting solution was stirred at room temperature 18 hours. The solution was diluted with water (35 mL) and the pH adjusted to 1 by the addition of 2.0 M aqueous hydrochloric acid solution. The mixture was then extracted with ethyl acetate and the combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford the title compound as a colourless solid (0.35 g).

^{1}H NMR (DMSO-d6): δ 4.17 (s, 2H), 4.97 (s, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.78 (dd, J = 1.8, 8.6 Hz, 1H), 7.98 (d, J = 8.6 Hz, 1H), 8.02 (s, 1H), 8.08 (d, J = 1.0 Hz, 1H), 12.94 (br s, 1H).
MS: ESI (+ve) (Method A): 362 $(M+H)^+$, Retention time 13.2 min.

Example 5: [2-(4-chlorobenzyl)quinazolin-8-yloxy]acetic acid



Preparation 5a: 2-(4-chlorobenzyl)-8-methoxy-3H-quinazolin-4-one

A mixture of 2-amino-3-methoxybenzoic acid (3.2 g), triethylamine (16 mL), 4-dimethylaminopyridine (0.24 g) and *N,N*-dimethylformamide (35 mL) at 0 °C was treated with (4-chlorophenyl)acetyl chloride (6.2 mL), and the resulting mixture was stirred at 0 °C for 30 minutes and then warmed to room temperature. The mixture was treated additional with acetyl chloride (3.0 mL) and triethylamine (5.0 mL) and then heated at 90 °C for 4.5 hours. The mixture was then treated portionwise with

ammonium carbonate (5.5 g) and heated at 90 °C for 18 hours and then cooled to room temperature and diluted with water (250 mL) and ethyl acetate (250 mL). The resulting precipitate was collected by filtration, washed with water and ethyl acetate and then dried to afford the title compound (2.8 g).

^{1}H NMR (DMSO-d6): δ 3.83 (s, 3H), 3.89 (s, 2H), 7.27-7.37 (m, 6H), 7.58 (d, J = 8.0 Hz, 1H), 12.39 (s, 1H).

Preparation 5b: 4-chloro-2-(4-chlorobenzyl)-8-methoxyquinazoline

A mixture of 2-(4-chlorobenzyl)-8-methoxy-3H-quinazolin-4-one (1.9 g), *N,N*-dimethylaniline (1.7 mL) and phosphorus oxychloride (6.2 mL) was heated at 80 °C under microwave irradiation for 15 minutes. The mixture was diluted with dichloromethane and poured onto a saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with 1.0 M aqueous hydrochloric acid solution, water and a saturated aqueous sodium hydrogen carbonate solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with dichloromethane to afford an orange waxy solid. Trituration with diethyl ether gave the title compound as an orange solid (1.3 g).

^{1}H NMR (DMSO-d6): δ 3.88 (s, 3H), 4.01 (s, 2H), 7.35-7.45 (m, 6H), 7.61 (dd, J = 1.3, 7.8 Hz, 1H).

Preparation 5c: 2-(4-chlorobenzyl)-8-methoxyquinazoline

A mixture of 4-chloro-2-(4-chlorobenzyl)-8-methoxyquinazoline (1.6 g), palladium (10 wt. % on activated carbon, 0.27 g), triethylamine (1.1 mL) and ethyl acetate was stirred at room temperature for 30 minutes under an atmosphere of hydrogen. The mixture was filtered through hyflo and the filtrated concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (1:0 to 2:1 by volume) and then by flash chromatography on C-18 column, eluting with a mixture of acetonitrile and water (0:1 to 1:0 by volume) to afford the title compound (0.94 g).

MS: ESI (+ve) (Method C): 285 $(M+H)^+$, Retention time 3.8 min.

Preparation 5d: 2-(4-chlorobenzyl)quinazolin-8-ol

A solution of 2-(4-chlorobenzyl)-8-methoxyquinazoline (0.4 g) in dichloromethane (1.2 mL) at 0 °C was treated with a 1.0 M solution of boron tribromide in dichloromethane (4.2 mL), and the resulting solution was stirred at 40 °C for 24 hours. The solution was diluted with water (20 mL), pH adjusted to 14 by the addition of 1.0 M aqueous sodium hydroxide solution and then filtered. The pH of the filtrated was adjusted to 7 by the addition of 1.0 M aqueous hydrochloric acid solution, and the resulting precipitate was collected by filtration, washed with water and then dried to afford the title compound as a tan solid (0.30 g).

MS: ESI (+ve) (Method C): 271 $(M+H)^+$, Retention time 3.8 min.

Preparation 5e: [2-(4-chlorobenzyl)quinazolin-8-yloxy]acetic acid methyl ester

A mixture of 2-(4-chlorobenzyl)quinazolin-8-ol (0.29 g), *N,N*-dimethylformamide (2.0 mL) and potassium carbonate (0.44 g) was treated with methyl bromoacetate (0.15 mL), and the resulting mixture was stirred at room temperature for 3 days. The mixture was diluted with water, extracted with dichloromethane and the combined extracts were washed with water and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate (2:1 by volume) to afford the title compound as a pale yellow solid (0.17 g).

MS: ESI (+ve) (Method C): 343 $(M+H)^+$, Retention time 3.7 min.

Preparation 5f: [2-(4-chlorobenzyl)quinazolin-8-yloxy]acetic acid

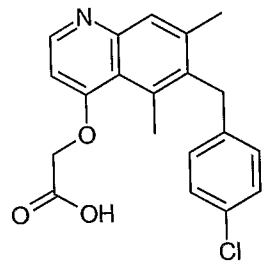
A mixture of [2-(4-chlorobenzyl)quinazolin-8-yloxy]acetic acid methyl ester (0.030 g), lithium hydroxide (0.010 g), tetrahydrofuran (1.0 mL) and water (1.0 mL) was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure, acidified by the addition of glacial acetic acid and the resulting precipitate was collected by filtration to afford the title compound as an off white solid (0.017 g).

^{1}H NMR (DMSO-d6): δ 4.33 (s, 2H), 4.64 (s, 2H), 7.21 (dd, J = 1.7, 7.3 Hz, 1H), 7.28-7.34 (m, 4H), 7.49 -7.55 (m, 2H), 9.42 (s, 1H).

MS: ESI (+ve) (Method A): 328 $(M+H)^+$, Retention time 9.8 min.

MS: ESI (+ve) (Method B): 328 $(M+H)^+$, Retention time 3.1 min.

Example 6: [6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-yloxy]acetic acid



Preparation 6a: *N*-[4-(4-chlorobenzoyl)-3,5-dimethylphenyl]acetamide

A mixture of *N*-(3,5-dimethylphenyl)acetamide (1.6 g) and aluminium trichloride (5.3 g) was treated dropwise with 4-chlorobenzoyl chloride (3.5 g), and the resulting mixture was stirred at room temperature for 30 minutes and then at 115 °C for 2 hours. The mixture was cooled to room temperature, slowly poured onto a mixture of ice and water and extracted with dichloromethane. The combined extracts were washed with a 6.0 M aqueous hydrochloric acid solution and a saturated aqueous sodium hydrogen carbonate solution and then dried over sodium sulfate. The solvent was removed under reduced pressure and the residue crystallised from a mixture of ethyl acetate and pentane to afford the title compound (2.4 g).

^{1}H NMR ($CDCl_3$): δ 2.08 (s, 6H), 2.20 (s, 3H), 7.24 (s, 2H), 7.32 (br s, 1H), 7.42, (d, J = 8.6 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H).

MS: ESI (+ve) (Method B): 302 $(M+H)^+$, Retention time 3.6 min.

Preparation 6b: (4-amino-2,6-dimethylphenyl)-(4-chlorophenyl)methanone

A mixture of *N*-[4-(4-chlorobenzoyl)-3,5-dimethylphenyl]acetamide (1.1 g), 6.0 M aqueous hydrochloric acid solution (3.0 mL) and ethanol (1.0 mL) was heated at reflux for 1 hour. The mixture was cooled to room temperature, neutralised by the slow addition of a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined extracts were washed with a saturated

aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure to afford the title compound as a yellow oil (0.98 g).

^{1}H NMR ($CDCl_3$): δ 2.02 (s, 6H), 3.73 (br s, 2H), 6.39 (s, 2H), 7.41, (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H).

Preparation 6c: 4-(4-chlorobenzyl)-3,5-dimethylphenylamine

Lithium aluminium hydride (1.3 g) at 0 °C was treated dropwise over a period of 15 minutes with a solution of aluminium trichloride (4.6 g) in diethyl ether (50 mL), and the resulting mixture was stirred at 0 °C for 5 minutes. The mixture was treated dropwise with a solution of (4-amino-2,6-dimethylphenyl)-(4-chlorophenyl)methanone (0.90 g) in diethyl ether (50 mL), and the resulting mixture was stirred at room temperature for 10 minutes. The mixture was diluted with a 6.0 M aqueous hydrochloric acid solution, followed by saturated aqueous sodium hydrogen carbonate solution and then extracted with ethyl acetate. The aqueous phase was further extracted with diethyl ether and the combined extracts were washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure to afford the title compound (0.89 g).

^{1}H NMR ($CDCl_3$): δ 2.12 (s, 6H), 3.27 (br s, 2H), 3.90 (s, 2H), 6.42 (s, 2H), 6.94 (d, J = 8.5 Hz, 2H), 7.18 (d, J = 8.6 Hz, 2H).

Preparation 6d: 5-{[4-(4-chlorobenzyl)-3,5-dimethylphenylamino]methylene}-2,2-dimethyl[1,3]dioxane-4,6-dione

A mixture of of 4-(4-chlorobenzyl)-3,5-dimethylphenylamine (0.89 g), 2,2-dimethyl-1,3-dioxane-4,6-dione (0.63 g), triethylorthoformate (0.64 g) and ethanol (35 mL) was heated at reflux for 1 hour. The mixture was cooled to room temperature, filtered and concentrated under reduced pressure. The residue was triturated with ethanol to afford the title compound (0.49 g).

MS: ESI (+ve) (Method B): 342 $(M+H)^+$, Retention time 4.3 min.

Preparation 6e: 6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-ol

5-{[4-(4-chlorobenzyl)-3,5-dimethylphenylamino]methylene}-2,2-dimethyl[1,3] dioxane-4,6-dione (0.3 g) was slowly added to Dowtherm A (4.0 mL) at 250 °C, and resulting mixture was stirred at 250 °C for 25 minutes. The mixture was cooled to room temperature, diluted with diethyl ether, and the resulting precipitate was collected by filtration to give the title compound as a yellow powder (0.18 g).

^{1}H NMR (DMSO-d6): δ 2.25 (s, 3H), 2.75 (s, 3H), 4.08 (s, 2H), 5.91 (d, J = 7.1 Hz, 1H), 6.99 (d, J = 8.6 Hz, 2H), 7.19 (s, 1H), 7.31 (d, J = 8.6 Hz, 2H), 7.70 (dd, J = 5.7, 7.1 Hz, 1H), 11.40 (br s, 1H).
MS: ESI (+ve) (Method B): 296 $(M+H)^+$, Retention time 3.2 min.

Preparation 6f: [6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-yloxy]acetic acid methyl ester

A mixture of 6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-ol (0.18 g), methyl bromoacetate (0.45 g), potassium carbonate (0.24 g) and *N,N*-dimethylformamide (3.0 mL) was heated at 80 °C for 1 hour. The mixture was cooled to room temperature and partitioned between water and dichloromethane. The organic phase was separated and the aqueous phase was extracted with ethyl acetate and dichloromethane. The combined organic phases were washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash 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 (0.16g).

^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.87 (s, 3H), 3.81 (s, 3H), 4.12 (s, 2H), 4.72 (s, 2H), 6.22 (d, J = 7.7 Hz, 1H), 6.82 (s, 1H), 6.92 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 7.7 Hz, 1H).

Preparation 6g: [6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-yloxy]acetic acid

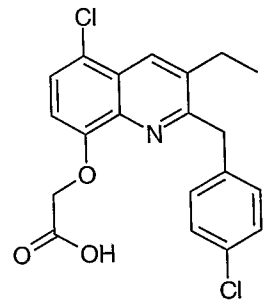
A mixture of [6-(4-chlorobenzyl)-5,7-dimethylquinolin-4-yloxy]acetic acid methyl ester (0.37 g), 1.0 M aqueous lithium hydroxide solution (2.0 mL) and tetrahydrofuran (10 mL) was stirred at room temperature for 1 hour. The mixture was acidified by the addition of a 1.0 M aqueous hydrochloric acid solution and concentrated under reduced pressure. The residue was triturated with a mixture of acetonitrile and water

(3:10 by volume) and the resulting precipitate was collected by filtration to afford the title compound as a white solid (0.12 g).

^{1}H NMR (DMSO-d6): δ 2.28 (s, 3H), 2.71 (s, 3H), 4.09 (s, 2H), 5.07 (s, 2H), 6.12 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.5 Hz, 2H), 7.21 (s, 1H), 7.27 (d, J = 8.5 Hz, 2H) 7.87 (d, J = 7.6 Hz, 1H), 13.3 (br s, 1H).

MS: ESI (+ve) (Method A): 354 $(M+H)^+$, Retention time 9.2 min.

Example 7: [5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-yloxy]acetic acid



Preparation 7a: 5-chloro-2-(4-chlorobenzyl)-3-hydroxy-8-methoxyquinoline-4-carboxylic acid

A 6.0 M aqueous potassium hydroxide solution (15 mL) at 100 °C was treated with 4-chloro-7-methoxyisatin (2.1 g) over a period of 15 minutes. The temperature was adjusted to 70 °C, and a solution of 3-(4-chlorophenyl)-2-oxopropyl acetate (3.4 g) in methanol (30 mL) was added slowly over 1 hour. The resulting mixture was heated at 70 °C overnight, cooled to room temperature and concentrated to low bulk under reduced pressure. The aqueous residue was filtered through hyflo and the pH of the filtrate was adjusted to 2 by the addition of aqueous hydrochloric acid solution. The resulting precipitate was collected by filtration to afford the title compound as a tan solid (0.5 g).

MS: ESI (+ve) (Method B): 378 $(M+H)^+$, Retention time 3.3 min.

Preparation 7b: 5-chloro-2-(4-chlorobenzyl)-8-methoxyquinolin-3-ol

A mixture of 5-chloro-2-(4-chlorobenzyl)-3-hydroxy-8-methoxyquinoline-4-carboxylic acid (0.5 g) and toluene (50 mL) was stirred at 75 °C for 15 minutes, then at 100 °C

for 30 minutes and then at 115 °C for 15 minutes. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture cyclohexane and dichloromethane (1:0 to 0:1 by volume) to afford the title compound as a yellow solid (0.12 g).

MS: ESI (+ve) (Method B): 334 $(M+H)^+$, Retention time 3.7 min.

Preparation 7c: methanesulfonic acid 5-chloro-2-(4-chlorobenzyl)-8-methoxyquinolin-3-yl ester

A mixture of 5-chloro-2-(4-chlorobenzyl)-8-methoxyquinolin-3-ol (0.11 g), dichloromethane (10 mL) and 2,6-dimethylpyridine (0.28 g) at -35 °C was treated dropwise with trifluoromethanesulfonic anhydride (0.37 g), and the resulting mixture was warmed to -5 °C over 30 minutes. The mixture was diluted with a 1.0 M aqueous hydrochloric acid solution. The organic phase was separated and washed with a 1.0 M aqueous hydrochloric acid solution and water and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:0 to 6:4 by volume) to afford the title compound (0.14 g).

MS: ESI (+ve) (Method C): 466 $(M+H)^+$, Retention time 4.8 min.

Preparation 7d: 5-chloro-2-(4-chlorobenzyl)-3-ethyl-8-methoxyquinoline

A mixture of methanesulfonic acid 5-chloro-2-(4-chlorobenzyl)-8-methoxyquinolin-3-yl ester (0.17 g), ethyl boronic acid (0.070 g), $KF.2H_2O$ (0.21 g), sodium bromide (0.056 g), tetrakis(triphenylphosphine)palladium(0) (0.10 g) and toluene (15 mL) was heated under argon at 115 °C for 30 minutes. The mixture was filtered through hyflo and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:1 by volume) to afford the title compound as a white solid (0.10 g).

MS: ESI (+ve) (Method B): 346 $(M+H)^+$, Retention time 4.5 min.

Preparation 7e: 5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-ol

A solution of 5-chloro-2-(4-chlorobenzyl)-3-ethyl-8-methoxyquinoline (0.10 g) in dichloromethane (5.0 mL) at -35 °C was treated dropwise with a 1.0 M solution of boron tribromide in dichloromethane (2.0 mL), and the resulting mixture was stirred at room temperature for 24 hours. The mixture was diluted with dichloromethane and a saturated aqueous sodium hydrogen carbonate solution. The organic phase was separated, washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with ethyl acetate to afford the title compound as a yellow solid (0.085 g).

MS: ESI (+ve) (Method B): 332 $(M+H)^+$, Retention time 4.9 min.

Preparation 7f: [5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-yloxy]acetic acid methyl ester

A mixture of 5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-ol (0.085 g), potassium carbonate (0.530 g) and acetonitrile (15 mL) was treated dropwise with methyl bromoacetate (0.58 g), and the resulting mixture was stirred at room temperature overnight. The mixture was filtered through hyflo and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with an aqueous hydrochloric acid solution and water and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (85:15 by volume) to afford the title compound (0.052 g).

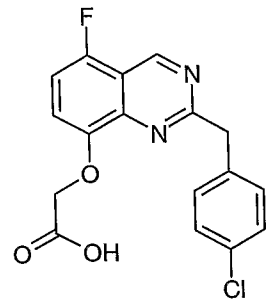
MS: ESI (+ve) (Method B): 404 $(M+H)^+$, Retention time 4.7 min.

Preparation 7g: [5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-yloxy]acetic acid

A mixture of [5-chloro-2-(4-chlorobenzyl)-3-ethylquinolin-8-yloxy]acetic acid methyl ester (0.050 g), 1.0 M aqueous sodium hydroxide solution (0.5 mL) and methanol (9.0 mL) was stirred at room temperature for 3 hours. The mixture was acidified by the addition of a 1.0 M aqueous hydrochloric acid solution and concentrated to low bulk under reduced pressure. The resulting precipitate was collected by filtration to afford the title compound (0.047 g).

^{1}H NMR (DMSO-d6): δ 1.13 (t, J = 7.4 Hz, 3H), 2.74 (q, J = 7.4 Hz, 2H), 4.35 (s, 2H), 4.90 (s, 2H), 7.00 (d, J = 8.5 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.5 Hz, 1H), 8.16 (s, 1H), 13.0 (br s, 1H).
MS: ESI (+ve) (Method A): 390 $(M+H)^+$, Retention time 12.4 min.

Example 8: [2-(4-chlorobenzyl)-5-fluoroquinazolin-8-yloxy]acetic acid



Preparation 8a: 6-fluoro-3-methoxy-2-nitrobenzonitrile

A mixture of 2-fluoro-5-methoxybenzonitrile (5.0 g) and acetic anhydride (76 g) at 0 °C was treated dropwise with fuming nitric acid (21 g), and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was poured onto a mixture of ice and water and extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous sodium hydrogen carbonate solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 0:1 by volume) to afford the title compound as a yellow solid (3.6 g).

^{1}H NMR ($CDCl_3$): δ 3.96 (s, 3H), 7.34 (dd, J = 4.3, 9.4 Hz, 1H), 7.40 (dd, J = 7.4, 9.4 Hz, 1H).

Preparation 8b: 2-amino-6-fluoro-3-methoxybenzonitrile

A mixture of 6-fluoro-3-methoxy-2-nitrobenzonitrile (2.4 g), glacial acetic acid (98 g) and water (0.2 mL) at 0 °C was treated with iron powder (3.5 g), and the resulting mixture was stirred at room temperature for 16 hours. The mixture was filtered through hyflo and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate, washed with a saturated aqueous sodium carbonate

solution and a 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 beige solid (1.9 g).

^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H), 4.71 (br s, 2H), 6.37 (t, J = 8.8 Hz, 1H), 6.78 (dd, J = 8.8, 4.8 Hz, 1H).

Preparation 8c: 2-(4-chlorophenyl)-*N*-(2-cyano-3-fluoro-6-methoxyphenyl)acetamide

A mixture of 2-amino-6-fluoro-3-methoxybenzonitrile (1.6 g) and pyridine (40 mL) at 0 °C was treated dropwise with a solution of (4-chlorophenyl)acetyl chloride (3.7 g) in dichloromethane (10 mL), and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was diluted with water and concentrated to low bulk under reduced pressure. The aqueous residue was extracted with ethyl acetate and the combined extracts were washed with water, 1.0 M aqueous hydrochloric acid solution and saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was triturated with diethyl ether. The resulting precipitate was collected by filtration to afford the title compound as a yellow solid (1.9 g).

^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 3.80 (s, 2H), 7.01 (d, J = 3.5 Hz, 1H), 7.03 (d, J = 1.4 Hz, 1H), 7.11 (br s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.38 (d, J = 8.5 Hz, 1H).

Preparation 8d: 2-(4-chlorobenzyl)-5-fluoro-8-methoxy-3H-quinazolin-4-one

A mixture of 2-(4-chlorophenyl)-*N*-(2-cyano-3-fluoro-6-methoxyphenyl)acetamide (1.0 g) and ethanol (8.0 mL) was treated with a solution of sodium hydroxide (1.5 g) in water (6.0 mL) and a solution of hydrogen peroxide in water (30%, 2.1 mL). The resulting mixture was heated at 80 °C for 18 hours, cooled to temperature and concentrated to low bulk under reduced pressure. The aqueous residue was diluted with water, cooled to 0 °C and the pH adjusted to 5-6 by the addition of glacial acetic acid. The resulting precipitate was collected by filtration and dried to afford the title compound as a white solid (0.47 g).

MS: ESI (+ve) (Method B): 319 $(M+H)^+$, Retention time 3.0 min.

Preparation 8e: methanesulfonic acid 2-(4-chlorobenzyl)-5-fluoro-8-methoxyquinazolin-4-yl ester

A mixture of 2-(4-chlorobenzyl)-5-fluoro-8-methoxy-3H-quinazolin-4-one (1.0 g), 2,6-lutidine (1.7 g) and dichloromethane (63 mL) at -25 °C was treated dropwise with trifluoromethanesulfonic anhydride (2.2 g), and the resulting mixture was warmed to -10 °C over 30 minutes. The mixture was diluted with a 1.0 M aqueous hydrochloric acid solution and the organic phase was separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash 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 (1.2 g).

MS: ESI (+ve) (Method B): 451 $(M+H)^+$, Retention time 4.5 min.

Preparation 8f: 2-(4-chlorobenzyl)-5-fluoro-8-methoxyquinazoline

A mixture of methanesulfonic acid 2-(4-chlorobenzyl)-5-fluoro-8-methoxyquinazolin-4-yl ester (0.90 g), ethyl acetate (20 mL), triethylamine (1.0 g) and palladium (10 wt. % on activated carbon, 0.21 g) was stirred at room temperature for 15 minutes under an atmosphere of hydrogen. The mixture was filtered through hyflo and the filtrate was washed with a saturated aqueous ammonium chloride solution and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with ethyl acetate to afford the title compound as a yellow solid (0.54 g).

MS: ESI (+ve) (Method B): 303 $(M+H)^+$, Retention time 3.7 min.

Preparation 8g: 2-(4-chlorobenzyl)-5-fluoroquinazolin-8-ol

A mixture of 2-(4-chlorobenzyl)-5-fluoro-8-methoxyquinazoline (0.34 g) and dichloromethane (3.4 mL) at 0 °C was treated dropwise with a 1.0 M solution of boron tribromide in dichloromethane (4.5 mL), and the resulting mixture was stirred at 0 °C for 1 hour. The mixture was diluted with a saturated aqueous sodium hydrogen carbonate solution and stirred a room temperature overnight. The mixture was

concentrated under reduced pressure and the aqueous residue was extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate to afford the title compound as a yellow solid (0.18 g).

^{1}H NMR (DMSO-d6): δ 4.40 (s, 2H), 7.23-7.28 (m, 1H), 7.30-7.41 (m, 5H), 9.59 (s, 1H), 10.1 (s, 1H).
MS: ESI (+ve) (Method B): 289 $(M+H)^+$, Retention time 3.7 min.

Preparation 8h: [2-(4-chlorobenzyl)-5-fluoroquinazolin-8-yloxy]acetic acid methyl ester

A mixture of 2-(4-chlorobenzyl)-5-fluoroquinazolin-8-ol (0.18 g), potassium carbonate (0.25 g) and *N,N*-dimethylformamide (1.2 mL) was treated dropwise with methyl bromoacetate (0.10 g), and the resulting mixture was stirred at room temperature for 30 minutes. The mixture was filtered through hyflo and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (1:0 to 3:7 by volume) to afford the title compound as a white solid (0.13 g).

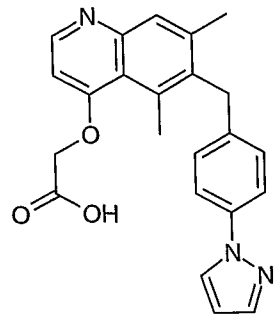
^{1}H NMR (DMSO-d6): δ 3.71 (s, 3H), 4.40 (s, 2H), 5.08 (s, 2H), 7.32-7.44 (m, 6H), 9.64 (s, 1H).
MS: ESI (+ve) (Method B): 361 $(M+H)^+$, Retention time 3.7 min.

Preparation 8i: [2-(4-chlorobenzyl)-5-fluoroquinazolin-8-yloxy]acetic acid

The title compound was prepared by the method of Preparation 6g using [2-(4-chlorobenzyl)-5-fluoroquinazolin-8-yloxy]acetic acid methyl ester.

^{1}H NMR (DMSO-d6): δ 4.37 (d, 2H), 4.88 (d, 2H), 7.21-7.42 (m, 6H), 9.59 (s, 1H).
MS: ESI (+ve) (Method B): 347 $(M+H)^+$, Retention time 3.3 min

Example 9: [5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-yloxy]acetic acid



Preparation 9a: *N*-[4-(4-fluorobenzoyl)-3,5-dimethylphenyl]acetamide

The title compound was prepared by the method of Preparation 6a using *N*-(3,5-dimethylphenyl)acetamide and 4-fluorobenzoyl chloride.

^{1}H NMR ($CDCl_3$): δ 2.09 (s, 6H), 2.20 (s, 3H), 7.12 (m, 3H), 7.82 (m, 2H), 7.25 (m, 2H).

Preparation 9b: *N*-[3,5-dimethyl-4-(4-pyrazol-1-ylbenzoyl)phenyl]acetamide

A mixture of pyrazole (0.041 g), potassium carbonate (0.083 g) and *N,N*-dimethylformamide (5.0 mL) was treated with *N*-[4-(4-fluorobenzoyl)-3,5-dimethylphenyl]acetamide (0.14 g), and the resulting mixture was stirred at room temperature for 2 hours and then stirred at 120 °C for 24 hours. The mixture was treated with additional potassium carbonate (0.02 g) and stirred at 120 °C for 2 hours. The mixture was then treated with additional potassium carbonate (0.035 g) and pyrazole (0.017g) and then stirred at 120 °C for 2 days. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by crystallisation from a mixture of ethyl acetate and pentane to afford the title compound (0.11 g).

^{1}H NMR ($CDCl_3$): δ 2.13 (s, 6H), 2.07 (s, 3H), 6.52 (t, J = 1.8, 2.5 Hz, 1H), 7.17 (br s, 1H), 7.26 (m, 2H), 7.77 (d, J = 1.7 Hz, 1H), 7.79 (d, J = 8.7 Hz, 2H), 7.90 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 2.5 Hz, 1H).

Preparation 9c: (4-amino-2,6-dimethylphenyl)-(4-pyrazol-1-ylphenyl)methanone

The title compound was prepared by the method of Preparation 6b using *N*-[3,5-dimethyl-4-(4-pyrazol-1-ylbenzoyl)phenyl]acetamide.

^{1}H NMR ($CDCl_3$): δ 2.05 (s, 6H), 3.17 (br s, 2H), 6.41 (s, 2H), 6.51 (dd, J = 1.9, 2.4 Hz, 1H), 7.78 (m, 3H), 7.91 (d, J = 8.7 Hz, 2H), 8.01 (d, J = 2.4 Hz, 1H).

Preparation of 9d: 3,5-dimethyl-4-(4-pyrazol-1-ylbenzyl)phenylamine

The title compound was prepared by the method of Preparation 6c using (4-amino-2,6-dimethylphenyl)-(4-pyrazol-1-ylphenyl)methanone.

MS: ESI (+ve) (Method B): 278 $(M+H)^+$, Retention time 2.6 min.

Preparation 9e: 5-{[3,5-dimethyl-4-(4-pyrazol-1-ylbenzyl)phenylamino]methylene}-2,2-dimethyl[1,3]dioxane-4,6-dione

The title compound was prepared by the method of Preparation 6d using 3,5-dimethyl-4-(4-pyrazol-1-ylbenzyl)phenylamine.

^{1}H NMR ($CDCl_3$): δ 1.76 (s, 6H), 2.28 (s, 6H), 4.07 (s, 2H), 6.44 (dd, J = 1.9, 2.4 Hz, 1H), 6.98 (s, 2H), 7.05 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 1.7 Hz, 1H), 7.87 (d, J = 2.5 Hz, 1H), 8.66 (d, J = 14.5 Hz, 1H), 11.19 (d, J = 14.5 Hz, 1H).

Preparation 9f: 5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-ol

The title compound was prepared by the method of Preparation 6e using 5-{[3,5-dimethyl-4-(4-pyrazol-1-ylbenzyl)phenylamino]methylene}-2,2-dimethyl[1,3]dioxane-4,6-dione.

^{1}H NMR ($CDCl_3$): δ 2.22 (s, 3H), 2.97 (s, 3H), 4.15 (s, 2H), 6.19 (d, J = 7.2 Hz, 1H), 6.42 (t, J = 2.1 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 7.23 (s, 1H), 7.47-7.54 (m, 3H), 7.68 (d, J = 1.7 Hz, 1H), 7.83 (d, J = 2.4 Hz, 1H), 11.48 (br s, 1H).
MS: ESI (+ve) (Method B): 296 $(M+H)^+$, Retention time 2.9 min.

Preparation 9g: [5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-yloxy]acetic acid methyl ester

The title compound was prepared by the method of Preparation 6f using 5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-ol.

^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.90 (s, 3H), 3.80 (s, 3H), 4.19 (s, 2H), 4.73 (s, 2H), 6.22 (d, J = 7.7 Hz, 1H), 6.43 (t, J = 2.1 Hz, 1H), 6.84 (s, 1H), 7.07 (d, J = 8.6 Hz, 2H), 7.30 (d, J = 7.7 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 1.7 Hz, 1H), 7.86 (d, J = 2.4 Hz, 1H).

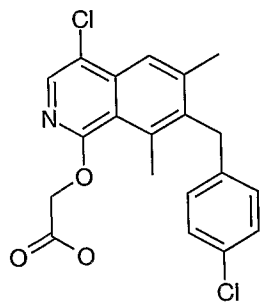
Preparation 9h: [5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-yloxy]acetic acid

The title compound was prepared by the method of Preparation 6g using [5,7-dimethyl-6-(4-pyrazol-1-ylbenzyl)quinolin-4-yloxy]acetic acid methyl ester.

^{1}H NMR (DMSO-d6): δ 2.27 (s, 3H), 2.74 (s, 3H), 4.10 (s, 2H), 4.85 (s, 2H), 5.90 (d, J = 7.7 Hz, 1H), 6.45 (t, J = 2.2 Hz, 1H), 7.03 (d, J = 8.5 Hz, 2H), 7.11 (s, 1H), 7.62-7.72 (m, 4H), 8.34 (d, J = 2.4 Hz, 1H).

MS: ESI (+ve) (Method A): 388 $(M+H)^+$, Retention time 8.1 min.

Example 10: [4-chloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinolin-1-yloxy]acetic acid



Preparation 10a: 5-benzyloxy-2-(4-chlorobenzyl)-1,3-dimethylbenzene

A mixture of (4-bromo-3,5-dimethyl)phenyl benzyl ether (0.21 g), 0.5 M solution of 4-chlorobenzyl zinc chloride (2.9 mL), tetrakis(triphenylphosphine)palladium (0.060 g) and *N,N*-dimethylformamide (10 mL) was heated at 90 °C for 20 hours. The mixture

was diluted with ethyl acetate, washed with saturated aqueous sodium hydrogen carbonate solution, 1.0 M aqueous hydrochloric acid solution and saturated sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:0 to 4:1 by volume). Further purification by flash chromatography on silica gel, eluting with a mixture of heptane and dichloromethane (53:47 by volume) gave the title compound as a waxy off-white solid (0.23 g).

^{1}H NMR ($CDCl_3$): δ 2.19 (s, 6H), 3.95 (s, 2H), 5.05 (s, 2H), 6.72 (s, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.29-7.48 (m, 5H).

Preparation 10b: 4-(4-chlorobenzyl)-3,5-dimethylphenol

A mixture of 5-benzyloxy-2-(4-chlorobenzyl)-1,3-dimethylbenzene (0.23 g), glacial acetic acid (8.0 mL) and 6.0 M aqueous hydrochloric acid solution (3.0 mL) was heated at 100 °C for 3 hours. The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with a mixture of heptane and dichloromethane (1:1 to 0:1 by volume) to afford the title compound as a colourless oil (0.14 g).

^{1}H NMR (CD_3OD): δ 2.13 (s, 6H), 3.95 (s, 2H), 6.53 (s, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H)

Preparation 10c: trifluoromethanesulfonic acid 4-(4-chlorobenzyl)-3,5-dimethylphenyl ester

A solution of 4-(4-chlorobenzyl)-3,5-dimethylphenol (0.89 g) and 2,6-lutidine (1.5 g) in dichloromethane (40 mL) at -30 °C was treated slowly with triflic anhydride (2.0 g), and the resulting mixture was stirred at -30 °C for 20 minutes. The mixture was warmed to 0 °C over 1 hour and then diluted with a 1.0 M aqueous hydrochloric acid solution. The organic phase was separated, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel,

eluting with a mixture of cyclohexane and dichloromethane (1:0 to 0:1 by volume) to afford the title compound as a colourless oil (1.1 g).

^{1}H NMR ($CDCl_3$): δ 2.25 (s, 6H), 4.00 (s, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.98 (s, 2H), 7.22 (d, J = 8.5 Hz, 2H).

Preparation 10d: (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acrylic acid ethyl ester

A mixture of trifluoromethanesulfonic acid 4-(4-chlorobenzyl)-3,5-dimethylphenyl ester (0.057 g), *N,N*-dimethylformamide (3.0 mL), tetrakis(triphenylphosphine) palladium (0.017 g), triethylamine (0.03 g) and acrylic acid ethyl ester (0.13 g) was stirred at 110 °C for 20 hours. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with a 1.0 M aqueous hydrochloric acid solution and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:0 to 0:1 by volume) to afford the title compound as a white solid (0.04 g).

^{1}H NMR ($CDCl_3$): δ 2.24 (s, 6H), 3.80 (s, 3H), 4.01 (s, 2H), 6.42 (d, J = 16.0 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.23 (s, 2H), 7.64 (d, J = 16.0 Hz, 1H).

Preparation 10e: (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acrylic acid

A solution of (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acrylic acid ethyl ester (0.039 g) in tetrahydrofuran (3.0 mL) and ethanol (2.0 mL) was treated with a 1.0 M aqueous lithium hydroxide solution (1.0 mL), and the resulting mixture was stirred at room temperature for 20 hours. The mixture was concentrated to low bulk, acidified by the addition of a 1.0 M aqueous hydrochloric acid solution and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure to afford the title compound as a pale yellow solid (0.037 g).

MS: ESI (+ve) (Method B): 299 $(M-H)^+$, Retention time 4.07 min.

Preparation 10f: (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acryloyl chloride

A solution of (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acrylic acid (0.48 g) in toluene (20 mL) was treated with thionyl chloride (2.0 mL), and the resulting mixture was heated at reflux for 5 hours. The mixture was concentrated under reduced pressure to give the title compound as a yellow solid (0.50 g).

^{1}H NMR (DMSO-d6): δ 2.21 (s, 6H), 4.02 (s, 2H), 6.47 (d, J = 16.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.39 (s, 1H), 7.51 (d, J = 16.0 Hz, 1H).

Preparation 10g: (*E*)-3-[4-(4-clorobenzyl)-3,5-dimethylphenyl]acryloyl azide

A mixture of sodium azide (0.04 g) and acetone (10 mL) at -10 °C was treated dropwise with a solution of (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acryloyl chloride (0.10 g) in acetone (10.0 mL), and the resulting mixture was stirred at 0 °C for 4 hours. The mixture was diluted with water and acetone and then concentrated to low bulk under reduced pressure. The resulting precipitate was collected by filtration to afford the title compound as yellow solid (0.085 g).

^{1}H NMR (DMSO-d_6): δ 2.21 (s, 6H), 4.03 (s, 2H), 6.65 (d, J = 15.9 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.49 (s, 2H), 7.68 (d, J = 15.9 Hz, 1H).

Preparation 10h: 7-(4-chlorobenzyl)-6,8-dimethyl-2H-isoquinolin-1-one

A mixture of diphenyl ether (3.0 mL) and tributylamine (1.0 mL) at 270 °C was treated portionwise over a period of 15 minutes with a mixture of (*E*)-3-[4-(4-chlorobenzyl)-3,5-dimethylphenyl]acryloyl azide (1.0 g) and diphenyl ether (5.0 mL), and the resulting mixture was stirred at 270 °C for 1.5 hours. The mixture was cooled to room temperature, diluted with heptane, and the resulting precipitate was collected by filtration to afford the title compound as a pale yellow solid (0.30 g).

MS: ESI (+ve) (Method B): 298 $(M+H)^+$, Retention time 3.9 min.

Preparation 10i: 4-chloro-7-(4-chlorobenzyl)-6,8-dimethyl-2H-isoquinolin-1-one

A solution of 7-(4-chlorobenzyl)-6,8-dimethyl-2H-isoquinolin-1-one (0.30 g) in dimethyl acetamide (6.0 mL) at 170 °C was treated portionwise with a solution of *N*-chlorosuccinimide (0.16 g) in dimethylacetamide (4.0 mL), and the resulting mixture was stirred at 170 °C for 45 minutes. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with a 1.0 M aqueous hydrochloric acid solution and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethyl acetate (1:0 to 8:2 by volume) to afford a solid. Trituration of the solid with acetonitrile gave the title compound as a pale brown solid (0.089 g).

MS: ESI (+ve) (Method B): 332 $(M+H)^+$, Retention time 4.3 min.

Preparation 10j: 1,4-dichloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinoline

A mixture of 4-chloro-7-(4-chlorobenzyl)-6,8-dimethyl-2H-isoquinolin-1-one (0.02 g) and phosphorus oxychloride (5.0 mL) was heated at 100 °C under microwave irradiation for 10 minutes. The mixture was poured onto a mixture of ice and water and extracted with ethyl acetate. The combine extracts were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash 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 pale yellow solid (0.011 g).

MS: ESI (+ve) (Method B): 350 $(M+H)^+$, Retention time 5.0 min.

Preparation 10k: [4-chloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinolin-1-yloxy]acetic acid ethyl ester

A mixture of 1,4-dichloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinoline (0.064 g), potassium carbonate (0.050 g), *N,N*-dimethylformamide (10 mL) and ethyl glycolate (0.65 g) was heated at 120 °C for 2 days. The mixture was cooled to room temperature, diluted with ethyl acetate and washed with a 1.0 M aqueous hydrochloric acid solution and a saturated aqueous sodium chloride solution and then dried over magnesium sulfate. The solvent was removed under reduced pressure to give the title compound.

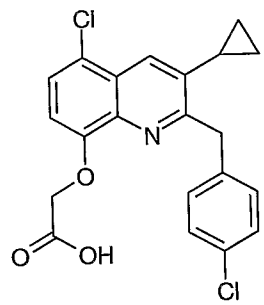
MS: ESI (+ve) (Method B): 418 $(M+H)^+$, Retention time 5.3 min.

Preparation 10l: [4-chloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinolin-1-yloxy]acetic acid

A mixture of [4-chloro-7-(4-chlorobenzyl)-6,8-dimethylisoquinolin-1-yloxy]acetic acid ethyl ester, tetrahydrofuran (5.0 mL) and 1.0 M aqueous lithium hydroxide solution (1.0 mL) was stirred at room temperature 1 hour. The mixture was concentrated under reduced pressure, pH adjusted to 3 by the addition of a 1.0 M aqueous hydrochloric acid solution and then extracted with ethyl acetate. The combined extracts were washed with a saturated aqueous sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford the title compound as a white solid.

MS: ESI (+ve) (Method B): 390 $(M+H)^+$, Retention time 4.5 min.

Example 11: [5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-yloxy]acetic acid



Preparation 11a: 5-chloro-2-(4-chlorobenzyl)-3-cyclopropyl-8-methoxyquinoline

A mixture of methanesulfonic acid 5-chloro-2-(4-chlorobenzyl)-8-methoxyquinolin-3-yl ester (0.075 g), cyclopropyl boronic acid (0.04 g), $KF.2H_2O$ (0.094 g), sodium bromide (0.025 g), tetrakis(triphenylphosphine)palladium(0) (0.05 g) and toluene (10.0 mL) was heated under argon at 111 °C for 2 hours. The mixture was treated with additional cyclopropyl boronic acid (0.040 g) and tetrakis(triphenylphosphine) palladium(0) (0.05 g) and then stirred at 111 °C for one hour. The mixture was filtered through hyflo and the filtrate was concentrated under reduced pressure. The residue

was purified by flash chromatography on silica gel, eluting with a mixture of cyclohexane and dichloromethane (1:0 to 0:1 by volume) to afford the title compound (0.06 g).

MS: ESI (+ve) (Method B): 358 $(M+H)^+$, Retention time 4.8 min.

Preparation 11b: 5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-ol

A solution of 5-chloro-2-(4-chlorobenzyl)-3-cyclopropyl-8-methoxyquinoline (0.06 g) in dichloromethane (10 mL) at -20 °C was treated dropwise with a 1.0 M solution of boron tribromide in dichloromethane (1.0 mL), and the resulting mixture was stirred at room temperature for 24 hours. The mixture was diluted with ethanol and concentrated under reduced pressure to afford the title compound (0.035 g).

MS: ESI (+ve) (Method B): 344 $(M+H)^+$, Retention time 5.1 min.

Preparation 11c: [5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-yloxy]acetic acid methyl ester

The title compound was prepared by the method of Preparation 7f using 5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-ol.

MS: ESI (+ve) (Method B): 416 $(M+H)^+$, Retention time 4.44 min.

Preparation 11d: [5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-yloxy]acetic acid

The title compound was prepared by the method of Preparation 7g using [5-chloro-2-(4-chlorobenzyl)-3-cyclopropylquinolin-8-yloxy]acetic acid methyl ester.

MS: ESI (+ve) (Method A): 402 $(M+H)^+$, Retention time 12.8 min.

^1H NMR (CD_3OD): δ 1.43-1.50 (m, 2H), 1.71-1.78 (m, 2H), 2.76-2.86 (m, 1H), 5.29 (s, 2H), 5.67 (s, 2H), 7.79 (d, J = 8.5 Hz, 1H), 8.02 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H), 8.35 (d, J = 8.5 Hz, 1H), 8.69 (s, 1H).

Biological Methods

Compounds of the invention of formula (I) were tested using the following biological test method to determine their ability to displace PGD_2 from the CRTH2 receptor.

CRTH2 Radioligand Binding Assay

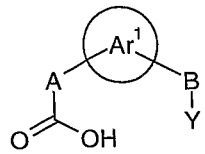
The receptor binding assay is performed in a final volume of 200 µL binding buffer [10 mM BES (pH 7.4), 1 mM EDTA, 10 mM manganese chloride, 0.01 % BSA] and 1 nM [^{3}H]-PGD_2 (Amersham Biosciences UK Ltd). Ligands are added in assay buffer containing a constant amount of DMSO (1 % by volume). Total 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.

Biological Results

All compounds of the Examples above were tested in the CRTH2 radioligand binding assay described above. All compounds have a K_i value of less than 10 µM in the binding assay; for example, Examples 6 and 7 have K_i value of 400 and 41 nM respectively.

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

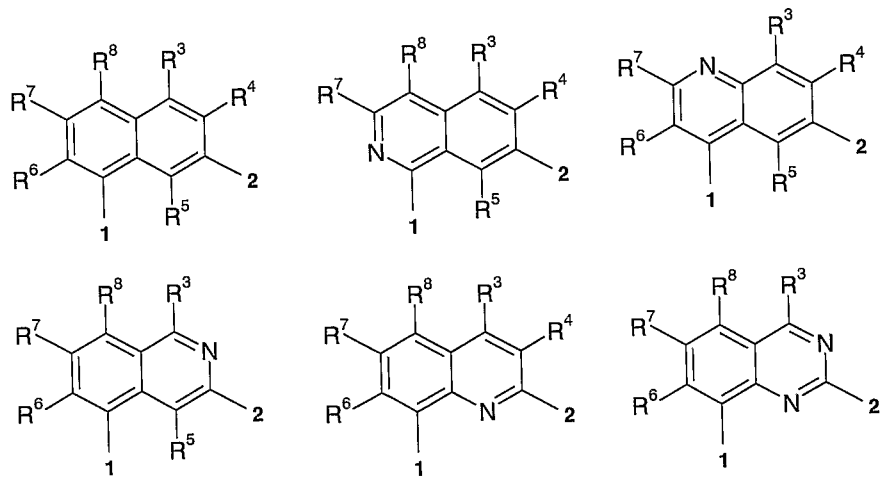
wherein:

A is selected from $-CR^1R^2-$, $-CR^1R^2CR^1R^2-$ or $-D(CR^1R^2)-$, wherein D is O, NR^1 or $S(O)_n$, and is attached to the Ar^1 ring;

R^1 and R^2 independently represent hydrogen or C_1-C_3alkyl;

B is $-CH_2-$, $-S(O)_n-$, or -O-;

Ar^1 is selected from one of the following formulae, wherein the bond marked 1 is attached to A while the bond marked 2 is attached to B;



R^3, R^4, R^5, R^6, R^7 and R^8 independently represent hydrogen, halogen, -CN, $-OR^9$, $-NR^{10}R^{11}$, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms;

R^9 is C_1-C_6alkyl or C_3-C_7cycloalkyl, optionally substituted by one or more fluoro atoms;

R^{10} and R^{11} independently represent hydrogen, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms;

Y is phenyl or 5- or 6-membered heteroaryl, wherein the phenyl or heteroaryl groups are optionally substituted by one or more substituents independently selected from halogen, -CN, $-S(O)_nR^9$, $-S(O)_2NR^{12}R^{13}$, $-NR^{12}S(O)_2R^9$ $-NR^{12}R^{13}$, $-NR^{12}COR^9$, $-CONR^{12}R^{13}$, $-COR^9$, $-OR^9$, C_1-C_6alkyl, C_3-C_7cycloalkyl, phenyl and 5- or 6-membered heteroaryl, wherein the alkyl substituents are optionally substituted with one or more fluoro atoms and the phenyl and 5- or 6-membered heteroaryl substituents are optionally substituted with one or more substituents independently selected from halogen, CN, C_1-C_6alkyl, C_3-C_7cycloalkyl, $-O(C_1$-C_6alkyl) or $-O(C_3$-C_7cycloalkyl), and wherein the alkyl substituents and alkyl part of the $-O(C_1$-C_6alkyl) substituent are optionally substituted with one or more fluoro atoms;

R^{12} and R^{13} independently represent hydrogen, C_1-C_6alkyl or C_3-C_7cycloalkyl, wherein the alkyl substituent is optionally substituted with one or more fluoro atoms; or R^{12} and R^{13} when attached to the same atom may form a 3-8 membered ring optionally containing one or more ring components selected from -O-, $-S(O)_n$- or $-NR^{14}$-, and optionally substituted with one or more fluoro or C_1-C_3 alkyl substituents;

R^{14} is hydrogen, C_1-C_6 alkyl, C_3-C_7cycloalkyl, $S(O)_2R^{15}$ or COR^{15};

R^{15} is C_1-C_6 alkyl or C_3-C_7cycloalkyl; and

n is 0, 1 or 2.

2. A compound as claimed in claim 1 wherein A is $-OCH_2$- or $-OCH(CH_3)$- wherein the oxygen is attached to the Ar^1 ring system.

3. A compound as claimed in claim 1 or claim 2 wherein B is $-CH_2$-.

4. A compound as claimed in any preceding claim, wherein Y is phenyl, optionally substituted as specified in claim 1.

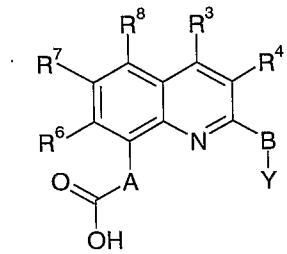
5. A compound as claimed in any of claims 1 to 3, wherein Y is a monocyclic 5- or 6-membered heteroaryl group, optionally substituted as specified in claim 1.

6. A compound as claimed in claim 4 or claim 5 wherein Y is substituted by chloro or pyrazolyl.

7. A compound as claimed in any of the preceding claims wherein R^4, R^5 and R^6 are independently selected from hydrogen, methyl, ethyl, isopropyl and cyclopropyl.

8. A compound as claimed in any of the preceding claims wherein R^7, R^8 and R^9 are independently selected from hydrogen, methyl, chloro, fluoro, bromo and trifluoromethyl.

9. A compound as claimed in claim 1 having the formula:



wherein A is $-OCH_2-$ or $-OCH(CH_3)-$ wherein the oxygen is attached to the ring carbon shown; B is $-CH_2-$, Y is as defined in claim 1; R^3 and R^4 are independently selected from hydrogen, methyl, ethyl, isopropyl and cyclopropyl; and R^6, R^7 and R^8 are independently selected from hydrogen, methyl, chloro, fluoro, bromo and trifluoromethyl.

10. A compound as claimed in claim 9 wherein Y is phenyl, substituted by choro or pyrazolyl.

11. A compound as claimed in any preceding claim, for use in therapy.

12. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 8, and a pharmaceutically acceptable carrier.

13. Use of a compound as claimed in any of claims 1 to 10, for the manufacture of a medicament for the treatment of asthma, chronic obstructive pulmonary disease, rhinitis, emphysema, allergic airway syndrome, or allergic rhinobronchitis.

14. Use of a compound as claimed in any of claims 1 to 10, for the manufacture of a medicament for the treatment of psoriasis, dermatitis, Crohn's disease, ulcerative colitis or irritable bowel disease.

15. A method of treatment of a condition selected from asthma, chronic obstructive pulmonary disease, rhinitis, allergic airway syndrome and allergic rhinobronchitis, comprising administering to a patient suffering such condition an effective amount of a compound as claimed in any of claims 1 to 10.

16. A method of treatment of a condition selected from psoriasis, dermatitis, Crohn's disease, ulcerative colitis and irritable bowel disease, comprising administering to a patient suffering such condition an effective amount of a compound as claimed in any of claims 1 to 10.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003758

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D215/28 C07D217/24 C07D239/74 C07D401/10 C07D215/233
A61K31/47 A61K31/4725 A61K31/517 A61P11/00 C07C59/66

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/036743 A (ARGENTA DISCOVERY LTD [GB]; CRAMP MICHAEL COLIN [GB]; ARIENZO ROSA [GB) 5 April 2007 (2007-04-05) cited in the application	1-16
Y	Table on pages 158-160 page 1, paragraph 1; claims 1,3,4,17; examples 1-79	1-16
Y	WO 2007/031747 A (ARGENTA DISCOVERY LTD [GB]; HYND GEORGE [GB]; RAY NICHOLAS CHARLES [GB) 22 March 2007 (2007-03-22) page 1, paragraph 1; claims 1,21,22; examples 1-22	1-16

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 2009	05/03/2009

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003758

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/007451 A (ASTRAZENECA AB [SE]; BONNERT ROGER [GB]; DICKINSON MARK [GB]; RASUL RU) 22 January 2004 (2004-01-22) page 16, paragraph 1 - page 17, paragraph 5; claims 1,8,12,13; examples 1-28	1-16
Y	WO 2007/125405 A (PFIZER PROD INC [US]; HUANG LIMING [US]; LIU SONG [US]; LUNNEY ELIZABE) 8 November 2007 (2007-11-08) page 12, paragraph 2; claims 1-3,12,14 examples page 15, lines 30-32	1-16
X	GB 2 253 846 A (ICI PLC [GB]) 23 September 1992 (1992-09-23) page 1, paragraph 1; claim 1; example 8	1,4

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Information on patent family members

International application No
PCT/GB2008/003758

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