(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2005 (29.12.2005)

PCT

(10) International Publication Number
WO 2005/123675 A1

(51) International Patent Classification⁷: **C07D 209/42**, 401/04, 401/14, A61K 31/404, A61P 29/00

(21) International Application Number: PCT/GB2005/002404

(22) International Filing Date: 17 June 2005 (17.06.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/580,403 18 June 2004 (18.06.2004) US

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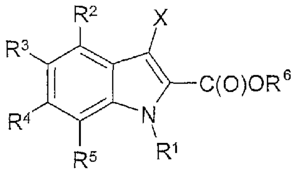
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: INDOLES USEFUL IN THE TREATMENT OF INFLAMMATION



(I)

(57) Abstract: There is provided a compound of formula (I), wherein X, R^1, R^2, R^3, R^4, R^5 and R^6 have meanings given in the description, and pharmaceutically-acceptable salts thereof, which compounds are useful in the treatment of diseases in which inhibition of the activity of microsomal prostaglandin E synthase-1 is desired and/or required, and particularly in the treatment of inflammation.

INDOLES USEFUL IN THE TREATMENT OF INFLAMMATION

Field of the Invention

This invention relates to novel pharmaceutically-useful compounds, which compounds are useful as inhibitors of enzymes belonging to the membrane-associated proteins in the eicosanoid and glutathione metabolism (MAPEG) family. Members of the MAPEG family include the microsomal prostaglandin E synthase-1 (mPGES-1), 5-lipoxygenase-activating protein (FLAP), leukotriene C_4 synthase and microsomal glutathione S-transferases (MGST1, MGST2 and MGST3). The compounds are of potential utility in the treatment of inflammatory diseases including respiratory diseases. The invention also relates to the use of such compounds as medicaments, to pharmaceutical compositions containing them, and to synthetic routes for their production

Background of the Invention

There are many diseases/disorders that are inflammatory in their nature. One of the major problems associated with existing treatments of inflammatory conditions is a lack of efficacy and/or the prevalence of side effects (real or perceived).

Inflammatory diseases that affect the population include asthma, inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, rhinitis, conjunctivitis and dermatitis.

Inflammation is also a common cause of pain. Inflammatory pain may arise for numerous reasons, such as infection, surgery or other trauma. Moreover, several diseases including malignancies and cardioavascular diseases are known to have inflammatory components adding to the symptomatology of the patients.

Asthma is a disease of the airways that contains elements of both inflammation and bronchoconstriction. Treatment regimens for asthma are based on the severity of the condition. Mild cases are either untreated or are only treated with inhaled ß-agonists which affect the bronchoconstriction element, whereas patients with more severe asthma typically are treated regularly with inhaled corticosteroids which to a large extent are anti-inflammatory in their nature.

Another common disease of the airways with inflammatory and bronchoconstrictive components is chronic obstructive pulmonary disease (COPD). The disease is potentially lethal, and the morbidity and mortality from the condition is considerable. At present, there is no known pharmacological treatment capable of changing the course of the disease.

The cyclooxygenase (COX) enzyme exists in two forms, one that is constitutively expressed in many cells and tissues (COX-1), and one that is induced by pro-inflammatory stimuli, such as cytokines, during an inflammatory response (COX-2).

COXs metabolise arachidonic acid to the unstable intermediate prostaglandin H_2 (PGH_2). PGH_2 is further metabolised to other prostaglandins including PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin and thromboxane A_2. These arachidonic acid metabolites are known to have pronounced physiological and pathophysiological activity including pro-inflammatory effects.

PGE_2 in particular is known to be a strong pro-inflammatory mediator, and is also known to induce fever and pain. Consequently, numerous drugs have been developed with a view to inhibiting the formation of PGE_2, including "NSAIDs" (non-steroidal antiinflammatory drugs) and "coxibs" (selective COX-2 inhibitors). These drugs act predominantly by inhibition of COX-1 and/or COX-2, thereby reducing the formation of PGE_2.

However, the inhibition of COXs has the disadvantage that it results in the reduction of the formation of all metabolites of arachidonic acid, some of which are known to have beneficial properties. In view of this, drugs which act by inhibition of COXs are therefore known/suspected to cause adverse biological effects. For example, the non-selective inhibition of COXs by NSAIDs may give rise to gastrointestinal side-effects and affect platelet and renal function. Even the selective inhibition of COX-2 by coxibs, whilst reducing such gastrointestinal side-effects, is believed to give rise to cardiovascular problems.

An alternative treatment of inflammatory diseases that does not give rise to the above-mentioned side effects would thus be of real benefit in the clinic. In particular, a drug that inhibits (preferably selectively) the transformation of PGH_2 to the pro-inflammatory mediator PGE_2 might be expected to reduce the inflammatory response in the absence of a corresponding reduction of the formation of other, beneficial arachidonic acid metabolites. Such inhibition would accordingly be expected to alleviate the undesirable side-effects mentioned above.

PGH_2 may be transformed to PGE_2 by prostaglandin E synthases (PGES). Two microsomal prostaglandin E synthases (mPGES-1 and mPGES-2), and one cytosolic prostaglandin E synthase (cPGES) have been described.

The leukotrienes (LTs) are formed from arachidonic acid by a set of enzymes distinct from those in the COX / PGES pathway. Leukotriene B4 is known to be a strong proinflammatory mediator, while the cysteinyl-containing leukotrienes C_4, D_4 and E_4 (CysLTs) are mainly very potent bronchoconstrictors and have thus been implicated in the pathobiology of asthma. The biological activities of the CysLTs are mediated through two receptors designated $CysLT_1$ and $CysLT_2$. As an alternative to steroids, leukotriene receptor antagonists (LTRas) have been developed in the treatment of asthma. These drugs may be given orally, but do not control inflammation satisfactorily. The presently used LTRas are highly selective for $CysLT_1$. It may be hypothesised that better control of asthma, and possibly also COPD, may be attained if the activity of both of the CysLT receptors could be reduced. This may be achieved by developing unselective LTRas, but also by inhibiting the activity of proteins, e.g. enzymes, involved in the synthesis of the CysLTs. Among these proteins, 5-lipoxygenase, 5-lipoxygenase-activating protein (FLAP), and leukotriene C_4 synthase may be mentioned. A FLAP inhibitor would also decrease the formation of the proinflammatory LTB_4.

mPGES-1, FLAP and leukotriene C_4 synthase belong to the membrane-associated proteins in the eicosanoid and glutathione metabolism (MAPEG) family. Other members of this family include the microsomal glutathione S-transferases (MGST1, MGST2 and MGST3). For a review, c.f. P.-J. Jacobsson *et al* in *Am. J. Respir. Crit. Care Med.* **161**, S20 (2000). It is well known that compounds prepared as antagonists to one of the MAPEGs may also exhibit inhibitory activity towards other family members, *c.f.* J. H Hutchinson *et al* in *J. Med. Chem.* **38**, 4538 (1995) and D. Claveau *et al* in *J. Immunol.* **170**, 4738 (2003). The former paper also describes that such compounds may also display notable cross-reactivity with proteins in the arachidonic acid cascade that do not belong to the MAPEG family, e.g. 5-lipoxygenase.

Thus, agents that are capable of inhibiting the action of mPGES-1, and thus reducing the formation of the specific arachidonic acid metabolite PGE_2, are likely to be of benefit in the treatment of inflammation. Further, agents that are capable of inhibiting the action of the proteins involved in the synthesis of the leukotrienes are also likely to be of benefit in the treatment of asthma and COPD.

Prior Art

Various indole-2-carboxylates, and derivatives thereof, have been disclosed in international patent applications WO 01/30343, WO 96/03377, WO 01/00197 and WO 99/33800, US patents Nos. 5,189,054 and 4,960,786, European patent application EP 483 881 and Italian Patent No. 1303260. However, none of these documents disclose or suggest the use of the indole-2-carboxylates in the treatment of inflammation.

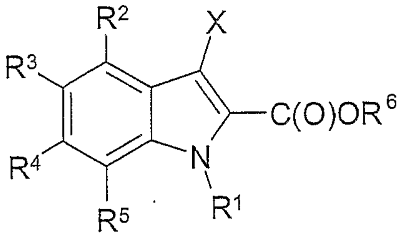
Similar indole-2-carboxylates have been disclosed for potential use in the treatment of inflammation in international patent applications WO 99/07678, WO 99/07351, WO 00/46198, WO 00/46197, WO 00/46195, WO 00/46199, WO 96/18393, WO 02/30895, WO 99/05104, WO 01/32621 and WO 2005/005415, US patents Nos. 5,081,145 and 5,081,138 and European patent applications EP 166 591 and EP 985 666. However, none of these documents disclose such compounds in which an aromatic group is directly attached to the ring system *via* the indole nitrogen.

International patent application WO 94/13662 and European patent application EP 186 367 also mention indoles for potential use in the treatment of inflammation. However, these documents do not mention or suggest compounds in which the benzenoid moiety of the indole is substituted with an aromatic ring.

International patent applications WO 94/14434, WO 99/43672, WO 98/08818, WO 99/43654 and WO 99/43651, and US patents Nos. 6,500,853 and 6,630,496 also describe structurally similar indoles for such potential use. However, there is no specific disclosure in any of these documents of indole-2-carboxylates in which an aromatic group is directly attached *via* the indole nitrogen.

Disclosure of the Invention

According to the invention there is provided a compound of formula I,



I

wherein

X and R^1 independently represent an aryl group or a heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from A;

one of the groups R^2, R^3, R^4 and R^5 represents an aryl group or a heteroaryl group (both of which are optionally substituted by one or more substituents selected from A) and:

a) the other groups are independently selected from hydrogen, G^1, an aryl group, a heteroaryl group (which latter two groups are optionally substituted by one or more substituents selected from A), C_{1-8} alkyl and a heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from G^1 and/or Z^1); and/or

b) any two other groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, a 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^6$, $-OR^6$ and =O;

A represents, on each occasion when mentioned above:

I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B;

II) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^1 and/or Z^1;

III) a G^1 group; or

IV) two A substituents may be linked together to form, along with at least two (e.g. adjacent) atoms of the aryl or heteroaryl group to which the two A substituents are attached, a further 3- to 5-membered ring, which ring optionally contains 1 to 3 (e.g. 1 or 2) hetereoatoms and/or 1 to 2 (e.g. 1) double bonds, and which is optionally substituted by halo or C_{1-8} alkyl, which latter group is optionally substituted by halo;

R^6 represents, on each occasion when mentioned above:

I) hydrogen;

II) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B; or

III) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^1 and/or Z^1;

G^1 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^7$;
wherein A^1 represents a single bond or a spacer group selected from $-C(O)A^2-$, $-S(O)_nA^3-$, $-N(R^8)A^4-$ or $-OA^5-$, in which:
A^2 and A^3 independently represent a single bond, -O-, $-N(R^8)-$ or -C(O)-;
A^4 and A^5 independently represent a single bond, -C(O)-, $-C(O)N(R^8)-$, -C(O)O-, $-S(O)_n-$ or $-S(O)_nN(R^8)-$;

Z^1 represents, on each occasion when mentioned above, =O, =S, $=NOR^7$, $=NS(O)_nN(R^8)(R^7)$, =NCN or $=C(H)NO_2$;

B represents, on each occasion when mentioned above:
I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^2, methylenedioxy, difluoromethylenedioxy and/or dimethylmethylenedioxy;
II) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^2 and/or Z^2;
III) a G^2 group; or
IV) methylenedioxy, difluoromethylenedioxy or dimethylmethylenedioxy;

G^2 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^6-R^9$;
wherein A^6 represents a single bond or a spacer group selected from $-C(O)A^7-$, $-S(O)_nA^8-$, $-N(R^{10})A^9-$ or $-OA^{10}-$, in which:
A^7 and A^8 independently represent a single bond, -O-, $-N(R^{10})-$ or -C(O)-;

A^9 and A^{10} independently represent a single bond, -C(O)-, -C(O)N(R^{10})-, -C(O)O-, -S(O)$_n$- or -S(O)$_n$N(R^{10})-;

Z^2 represents, on each occasion when mentioned above, =O, =S, =NOR^9, =NS(O)$_n$N(R^{10})(R^9) , =NCN or =C(H)NO$_2$;

R^7, R^8, R^9 and R^{10} are independently selected from:

i) hydrogen;

ii) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^3, methylenedioxy, difluoromethylenedioxy and/or dimethylmethylenedioxy;

iii) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by G^3 and/or Z^3; or

any pair of R^7 and R^8, or R^9 and R^{10}, may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms a further 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from G^3 and/or Z^3;

G^3 represents, on each occasion when mentioned above, halo, cyano, -N$_3$, -NO$_2$, -ONO$_2$ or -A^{11}-R^{11};

wherein A^{11} represents a single bond or a spacer group selected from -C(O)A^{12}-, -S(O)$_n$$A^{13}$-, -N($R^{12}$)$A^{14}$- or -O$A^{15}$-, in which:

A^{12} and A^{13} independently represent a single bond, -O-, -N(R^{12})- or -C(O)-;

A^{14} and A^{15} independently represent a single bond, -C(O)-, -C(O)N(R^{12})-, -C(O)O-, -S(O)$_n$- or -S(O)$_n$N(R^{12})-;

Z^3 represents, on each occasion when mentioned above, =O, =S, =NOR^{11}, =NS(O)$_n$N(R^{12})(R^{11}) , =NCN or =C(H)NO$_2$;

n represents, on each occasion when mentioned above, 1 or 2;

R^{11} and R^{12} are independently selected from:

i) hydrogen;

ii) C_{1-6} alkyl or a heterocycloalkyl group, both of which groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$, $-O(R^{13})$ and =O; and

iii) an aryl or heteroaryl group, both of which are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$ and $-O(R^{13})$; or

any pair R^{11} and R^{12} may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms a further 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$, $-O(R^{13})$ and =O;

R^{13} and R^{14} are independently selected from hydrogen and C_{1-4} alkyl, which latter group is optionally substituted by one or more halo groups;

or a pharmaceutically-acceptable salt thereof,

which compounds and salts are referred to hereinafter as "the compounds of the invention".

Pharmaceutically-acceptable salts include acid addition salts and base addition salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a compound of the invention in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

Compounds of the invention may contain double bonds and may thus exist as *E* (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation (i.e. a 'chiral pool' method), by reaction of the appropriate starting material with a 'chiral auxiliary' which can subsequently be removed at a suitable stage, by derivatisation (i.e. a resolution, including a dynamic resolution), for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means such as chromatography, or by reaction with an appropriate chiral reagent or chiral catalyst all under conditions known to the skilled person. All stereoisomers and mixtures thereof are included within the scope of the invention.

Unless otherwise specified, C_{1-q} alkyl groups (where q is the upper limit of the range) defined herein may be straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming a C_{3-q} cycloalkyl group). C_{3-q} cycloalkyl groups that may be mentioned include monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged. Further, when there is a sufficient number (i.e. a minimum of four) of carbon atoms, such groups may also be part cyclic. Such alkyl groups may also be saturated or, when there is a sufficient number (i.e. a minimum of two) of carbon atoms, be unsaturated (forming, for example, a C_{3-q} cycloalkenyl, a C_8 cycloalkynyl or, more particularly, a C_{2-q} alkenyl or a C_{2-q} alkynyl group). Further, in the case where the substituent is another cyclic compound, then the cyclic substituent may be attached through a single atom on the cycloalkyl group, forming a so-called "spiro"-compound.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Heterocycloalkyl groups that may be mentioned include those in which at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom), and in which the total number of atoms in the ring system is between three and twelve (e.g. between five and ten). Further, such heterocycloalkyl groups may be saturated or unsaturated containing one or more double and/or triple bonds, forming for example a C_{2-q} (e.g. C_{3-q}) heterocycloalkenyl (where q is the upper limit of the range) or a C_{3-q} heterocycloalkynyl group. C_{2-q} heterocycloalkyl groups that may be mentioned include aziridinyl, azetidinyl, dihydropyranyl, dihydropyridyl, dihydropyrrolyl (including 2,5-dihydropyrrolyl), dioxolanyl (including 1,3-

dioxolanyl), dioxanyl (including 1,3-dioxanyl and 1,4-dioxanyl), dithianyl (including 1,4-dithianyl), dithiolanyl (including 1,3-dithiolanyl), imidazolidinyl, imidazolinyl, morpholinyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl, thietanyl, thiiranyl, thiolanyl, thiomorpholinyl, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. Other heterocycloalkyl groups that may be mentioned include 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo-[3.2.1]octanyl, 8-azabicyclo[3.2.1]-octanyl, 7-oxabicyclo[2.2.1]heptanyl and 6-oxabicyclo[3.2.1]octanyl. Heterocycloalkyl groups that may be mentioned include monocyclic and bicyclic heterocycloalkyl groups, which groups may further be bridged. Substituents on heterocycloalkyl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. Further, in the case where the other substituent is another cyclic compound, then the cyclic compound may be attached through a single atom on the heterocycloalkyl group, forming a so-called "spiro"-compound. The point of attachment of heterocycloalkyl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. Heterocycloalkyl groups may also be in the *N*- or *S*- oxidised form.

For the avoidance of doubt, the term "bicyclic", when employed in the context of cycloalkyl and heterocycloalkyl groups refers to such groups in which the second ring is formed between two adjacent atoms of the first ring. The term "bridged", when employed in the context of cycloalkyl or heterocycloalkyl groups refers to monocyclic or bicyclic groups in which two non-adjacent atoms are linked by either an alkylene or heteroalkylene chain (as appropriate).

Aryl groups that may be mentioned include C_{6-13} (e.g. C_{6-10}) aryl groups. Such groups may be monocyclic or bicyclic and have between 6 and 13 (e.g. 10) ring carbon atoms, in which at least one ring is aromatic. C_{6-13} aryl groups include phenyl, naphthyl and the like, such as fluorenyl and, more particularly, 1,2,3,4-tetrahydronaphthyl, indanyl, and indenyl. The point of attachment of aryl groups may be *via* any atom of the ring system. However, when aryl groups are bicyclic or tricyclic, they are preferably linked to the rest of the molecule *via* an aromatic ring.

Heteroaryl groups that may be mentioned include those which have between 5 and 10 members. Such groups may be monocyclic, bicyclic or tricyclic, provided that at least one of the rings is aromatic and wherein at least one (e.g. one to four) of the atoms in the ring system is other than carbon (i.e. a heteroatom). Heterocyclic groups that may be mentioned include acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl (including 2,1,3-benzothiazolyl), benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzimidazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiaziolyl, isoxazolyl, naphthyridinyl (including 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-

tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heteroaryl groups may be *via* any atom in the ring system including (where appropriate) a heteroatom (such as a nitrogen atom), or an atom on any fused carbocyclic ring that may be present as part of the ring system. However, when heteroaryl groups are bicyclic or tricyclic, they are preferably linked to the rest of the molecule *via* an aromatic ring. Heteroaryl groups may also be in the *N*- or *S*- oxidised form.

Heteroatoms that may be mentioned include phosphorus, silicon, boron, tellurium, preferably, selenium and, more preferably oxygen, nitrogen and/or sulfur.

For the avoidance of doubt, optionally substituted methylenedioxy groups, when attached to a ring system, are formed between any two adjacent atoms of the ring system.

For the avoidance of doubt, in cases in which the identity of two or more substituents in a compound of the invention may be the same, the actual identities of the respective substituents are not in any way interdependent. For example, in the situation in which R^1 and X are both aryl groups substituted by one or more C_{1-8} alkyl groups, the alkyl groups in question may be the same or different. Similarly, when groups are substituted by more than one substituent as defined herein, the identities of those individual substituents are not to be regarded as being interdependent. For example, when X and/or R^1 represents e.g. an aryl group substituted by G^1

in addition to, for example, C_{1-8} alkyl, which latter group is substituted by G^1, the identities of the two G^1 groups are not to be regarded as being interdependent.

Compounds of the invention that may be mentioned include those in which:
A^2 and A^3 independently represent a single bond, -O- or -N(R^8)-;
Z^1 represents, on each occasion when mentioned above, =O, =NOR^7, =NS(O)$_n$N(R^8)(R^7), =NCN or =C(H)NO$_2$;
A^7 and A^8 independently represent a single bond, -O- or -N(R^{10})-;
Z^2 represents, on each occasion when mentioned above, =O, =NOR^9, =NS(O)$_n$N(R^{10})(R^9) , =NCN or =C(H)NO$_2$;
A^{12} and A^{13} independently represent a single bond, -O- or -N(R^{12})-; and/or
Z^3 represents, on each occasion when mentioned above, =O, =NOR^{11}, =NS(O)$_n$N(R^{12})(R^{11}) , =NCN or =C(H)NO$_2$.

Preferred compounds of the invention include those in which:
G^1 represents halo, cyano, -N$_3$, -NO$_2$ or -A^1-R^7;
A^4 and A^5 independently represent a single bond, -C(O)-, -C(O)N(R^8)- or -C(O)O-;
Z^1 represents =NOR^7, =NCN or, preferably, =O;
G^2 represents cyano, -N$_3$ or, more preferably, halo, -NO$_2$ or -A^6-R^9;
A^6 represents -N(R^{10})A^9- or -OA^{10}-;
A^9 represents -C(O)N(R^{10})-, -C(O)O- or, more preferably, a single bond or -C(O)-;
A^{10} represents A^9 and, preferably, a single bond;
Z^2 represents =NOR^9 or =NCN or, more preferably, =O;
G^3 represents halo, -NO$_2$ or -A^{11}-R^{11};
A^{11} represents -N(R^{12})- or -O-;
Z^3 represents =O;
n represents 2;

when either of R^{11} and R^{12} represent optionally substituted C_{1-6} alkyl, the optional substituent is one or more halo groups;
when either of R^{13} and R^{14} represent optionally substituted C_{1-4} alkyl, the optional substituent is one or more fluoro groups.

Preferred compounds of the invention include those in which R^1, X and (when they represent an aryl or a heteroaryl group) R^2, R^3, R^4 and/or R^5 represent an optionally substituted phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, imidazolyl (e.g 1-imidazolyl, 2-imidazolyl or 4-imidazolyl), oxazolyl, isoxazolyl, thiazolyl, pyridyl (e.g. 2-pyridyl, 3-pyridyl or 4-pyridyl), indazolyl, indolyl, indolinyl, isoindolinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinolizinyl, benzofuranyl, isobenzofuranyl, chromanyl, benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, benzimidazolyl, quinazolinyl, quinoxalinyl, 1,3-benzodioxolyl, benzothiazolyl, and/or benzodioxanyl, group. Other groups that may be mentioned include optionally substituted 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl and tetrazolyl.

Preferred values of R^1 include optionally substituted phenyl, naphthyl and pyridyl.

Preferred values of X include optionally substituted phenyl and pyridyl.

Preferred values of R^2, R^3, R^4 and R^5, when any one represents an aryl or a heteroaryl group, include optionally substituted phenyl and pyridyl.

Optional substituents on such R^1, X, R^2, R^3, R^4 and R^5 groups are preferably selected from:
cyano;

heterocycloalkyl, such as a 4 to 8 (e.g. 5 or 6) membered nitrogen-containing heterocycloalkyl group optionally containing a further heteroatom (e.g. a nitrogen or oxygen heteroatom) and optionally substituted by one or more halo or C_{1-3} alkyl (e.g. methyl) group, so forming, for example, a pyrrolidinyl, piperidinyl, piperazinyl or morpholinyl group; and, more preferably selected from:

halo (e.g. fluoro, chloro or bromo);

-NO_2;

C_{1-6} alkyl, which alkyl group may be linear or branched (e.g. C_{1-4} alkyl (including methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *t*-butyl), *n*-pentyl, isopentyl, *n*-hexyl or isohexyl), cyclic (e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl), part-cyclic (e.g. cyclopropylmethyl), unsaturated (e.g. 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 4-pentenyl or 5-hexenyl) and/or optionally substituted with one or more halo (e.g. fluoro) group (so forming, for example, fluoromethyl, difluoromethyl or trifluoromethyl);

-OR^{15}; and

-$N(R^{15})R^{16}$;

wherein R^{15} and R^{16} independently represent, on each occasion when mentioned above, H or C_{1-6} alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl or *t*-butyl (which alkyl groups are optionally substituted by one or more halo (e.g. fluoro) groups (so forming, for example, trifluoromethyl)).

Preferred values of R^6 include C_{1-4} alkyl and, particularly, H.

More preferred compounds include those in which:

X represents an aryl group such as a phenyl group or a heteroaryl group such as a pyridyl group, both of which are optionally substituted by one or two A groups;

R^1 represents an aryl group such as a phenyl or naphthyl group or a heteroaryl group such as a pyridyl group, both of which are optionally substituted by one or two A groups;

R^3 and R^4 independently represent G^1 or, more preferably, hydrogen, an aryl group, such as a phenyl group, or a heteroaryl group such as a pyridyl group, which latter two groups are optionally substituted by one or two A groups;

at least one of R^3 and R^4 represents optionally substituted aryl or heteroaryl, and up to one other represents G^1 or, more preferably, hydrogen;

when R^3 or R^4 represents an aryl or heteroaryl group, then the other substituents on the essential benzene ring of the compound of formula I (i.e. R^2, R^5 and R^3 or R^4 (as appropriate)) independently represent G^1 (e.g. halo (such as chloro), cyano, methyl, methoxy, trifluoromethyl or trifluoromethoxy) or, more preferably, hydrogen;

A represents G^1;

G^1 represents halo (e.g. chloro), cyano or, more preferably, $-NO_2$ or $-A^1-R^7$;

A^1 represents a single bond, $-N(R^8)A^4-$ or $-OA^5-$;

A^4 and A^5 independently represent a single bond;

R^7 and R^8 are independently selected from hydrogen and C_{1-6} alkyl, which latter group is optionally substituted by one or more substituents selected from G^3;

G^3 represents halo (especially fluoro).

Especially preferred compounds of the invention are wherein:

X represents a phenyl group, substituted, for example in the 3- or, preferably, 4-position, by a single $-A^1-R^7$ group. In such instances, A^1 may represent $-OA^5-$, in which A^5 is as hereinbefore defined and preferably a single bond. R^7 may, in such instances, represent C_{1-4} alkyl, such as an optionally branched propyl, so forming, for example, a 4-isopropoxyphenyl group. Alternatively, X may represent a pyridyl group (e.g. a 3-pyridyl group), optionally substituted, for example at the *meta*- or, preferably, the *para*-position relative to the point of attachment of the X group to the indole ring, with a single -A^1-R^7 group. In such instances A^1 may represent -OA^5- in which A^5 is as hereinbefore defined and, preferably, is a single bond and R^7 represents C_{1-4} alkyl, such as an optionally branched propyl group, so forming, for example a 6-isopropoxypyrid-3-yl or 3-pyridyl group;

R^6 represents hydrogen;

R^1 represents a naphthyl group (e.g. 2-naphthyl), preferably unsubstituted, or a phenyl group, substituted by an -A^1-R^7 group and, optionally, a further -NO_2 group. In such instances A^1 may represent -OA^5-, a single bond or -N(R^8)A^4-, in which A^4 and A^5 are as hereinbefore defined and are preferably single bonds. When A^1 represents -OA^5-, R^7 is preferably a C_{1-4} alkyl group, such as an optionally branched propyl group or a methyl group, optionally substituted by one or more G^3 group, in which G^3 is preferably halo (especially fluoro). When A^1 represents a single bond, R^7 is preferably a C_{1-2} alkyl group, such as methyl. When A^1 represents -N(R^8)A^4-, R^8 may represent H or C_{1-2} alkyl, such as methyl, and R^7 may represent C_{1-4} alkyl, such as ethyl or, preferably, methyl or optionally branched propyl. Thus R^1 may represent isopropoxyphenyl (e.g. 2-, 3- and 4-isopropoxyphenyl), 4-dimethylaminophenyl, 4-isopropylaminophenyl, 4-trifluoromethoxyphenyl or 4-methyl-3-nitrophenyl;

alternatively, R^1 may represent a pyridyl (e.g. a 2-pyridyl or 3-pyridyl) group, optionally substituted, for example by an -A^1-R^7 group. In such instances, A^1 may represent -OA^5- or a single bond, in which A^5 is as hereinbefore defined and preferably a single bond. When A^1 represents -OA^5-, R^7 is preferably a C_{1-4} alkyl group, for example a C_{1-3} alkyl group such as an optionally branched propyl group. When A^1 represents a single bond, R^7 is preferably a C_{1-2} alkyl group, such as methyl, optionally substituted by one or more G^3 group, in which G^3 is as hereinbefore defined and preferably a fluoro group. Thus R^1 may also represent 5-trifluoromethylpyrid-2-yl, 6-isopropoxypyrid-3-yl or 3-pyridyl;

R^2 represents H;

R^3 represents H, phenyl or pyridyl, which latter two groups are optionally substituted. For example, the phenyl group may be substituted in the 3- or, preferably, 4-position, by a single $-A^1-R^7$ group. In such instances, A^1 may represent a single bond or $-OA^5-$, wherein A^5 is preferably a single bond, and R^7 may represent C_{1-4} alkyl, such as methyl or optionally branched butyl, optionally substituted by one or more G^3 groups, in which G^3 is halo, such as fluoro. Thus R^3 may represent 4-*tert*-butylphenyl or 4-trifluoromethylphenyl;

R^4 represents H, phenyl or pyridyl, which latter two groups are optionally substituted. For example, the phenyl group may be substituted in the 3- or, preferably, 4-position, by a single $-A^1-R^7$ group. In such instances A^1 may represent
$-OA^5-$, in which A^5 is a single bond and R^7 represents a C_{1-4} alkyl group, preferably a C_{1-3} alkyl group, such as an optionally branched propyl group, which alkyl group is optionally substituted by one or more G^3 groups, in which G^3 is halo, such as fluoro. Thus R^4 may represent a 4-isopropoxyphenyl group;

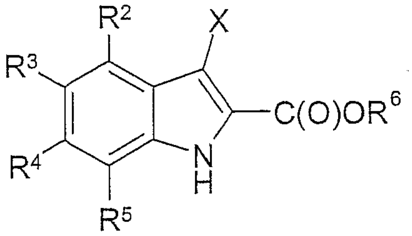
R^5 represents H.

Particularly preferred compounds of the invention include those of the examples described hereinafter.

Compounds of the invention may be made in accordance with techniques that are well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which process comprises:

(i) reaction of a compound of formula II,



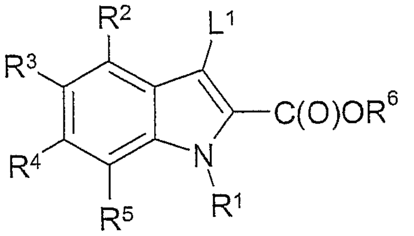
II

wherein X, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a compound of formula III,

R^1L^1 III

wherein L^1 represents a suitable leaving group such as chloro, bromo, iodo, a sulfonate group (e.g. $-OS(O)_2CF_3$, $-OS(O)_2CH_3$, $-OS(O)_2PhMe$ or a nonaflate) or $-B(OH)_2$ and R^1 is as hereinbefore defined, for example optionally in the presence of an appropriate metal catalyst (or a salt or complex thereof) such as Cu, $Cu(OAc)_2$, CuI (or CuI/diamine complex), $Pd(OAc)_2$, $Pd_2(dba)_3$ or $NiCl_2$ and an optional additive such as Ph_3P, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, xantphos, NaI or an appropriate crown ether such as 18-crown-6-benzene, in the presence of an appropriate base such as NaH, Et_3N, pyridine, *N,N'*-dimethylethylenediamine, Na_2CO_3, K_2CO_3, K_3PO_4, Cs_2CO_3, *t*-BuONa or *t*-BuOK (or a mixture thereof), in a suitable solvent (e.g. dichloromethane, dioxane, toluene, ethanol, isopropanol, dimethylformamide, ethylene glycol, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or a mixture thereof) or in the absence of an additional solvent when the reagent may itself act as a solvent (e.g. when R^1 represents phenyl and L^1 represents bromo, i.e. bromobenzene). This reaction may be carried out at room temperature or above (e.g. at a high temperature, such as the reflux temperature of the solvent system that is employed) or using microwave irradiation;

(ii) reaction of a compound of formula IV,



IV

wherein L^1, R^1, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a compound of formula V,

$$XL^2 \qquad \text{V}$$

wherein L^2 represents a suitable leaving group such as chloro, bromo, iodo, $-B(OH)_2$ or a protected derivative thereof, for example a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group, 9-borabicyclo[3.3.1]nonane (9-BBN), $-Sn(alkyl)_3$ (e.g. $-SnMe_3$ or $-SnBu_3$), or a similar group known to the skilled person, and X is as hereinbefore defined. The skilled person will appreciate that L^1 and L^2 will be mutually compatible. This reaction may be performed, for example in the presence of a suitable catalyst system, e.g. a metal (or a salt or complex thereof) such as CuI, $PdCl_2$, Pd/C, $Pd(OAc)_2$, $Pd(Ph_3P)_2Cl_2$, $Pd(Ph_3P)_4$, $Pd_2(dba)_3$ or $NiCl_2$ and an additive such as $t\text{-}Bu_3P$, $(C_6H_{11})_3P$, Ph_3P, $AsPh_3$, $P(o\text{-}Tol)_3$, 1,2-bis(diphenylphosphino)ethane, 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl, 2,2'-bis(diphenylphosphino)-

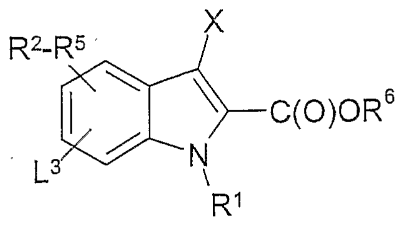
1,1'-binaphthyl, 1,1'-bis(diphenylphosphinoferrocene), 1,3-bis(diphenylphosphino)propane or xantphos, together with a suitable base such as, Na_2CO_3, K_3PO_4, Cs_2CO_3, KOH, NaOH, K_2CO_3, CsF, Et_3N, $(i\text{-Pr})_2NEt$, *t*-BuONa or *t*-BuOK (or mixtures thereof) in a suitable solvent such as dioxane, toluene, ethanol, dimethylformamide, ethylene glycol dimethyl ether, water, dimethylsulfoxide, acetonitrile, dimethylacetamide, *N*-methylpyrrolidinone, tetrahydrofuran or mixtures thereof. The reaction may also be carried out for example at room temperature or above (e.g. at a high temperature such as the reflux temperature of the solvent system) or using microwave irradiation. The skilled person will appreciate that when L^1 or L^2 (of the compounds of formulae IV and V, respectively, represent halo, such compounds may first be activated by:

(I) forming the corresponding Grignard reagent under standard conditions known to those skilled in the art (e.g. employing magnesium or a suitable reagent such as a mixture of C_{1-6} alkyl-Mg-halide and $ZnCl_2$ or LiCl), followed by reaction with a compound of formula IV or V (as appropriate), optionally in the presence of a catalyst (e.g. $FeCl_3$) under conditions known to those skilled in the art; or

(II) forming the corresponding lithiated compound under halogen-lithium exchange reaction conditions known to those skilled in the art (e.g. employing *n*-BuLi or *t*-BuLi in the presence of a suitable solvent (e.g. a polar aprotic solvent, such as THF)), followed by reaction with a compound of formula IV or V (as appropriate).

The skilled person will also appreciate that the magnesium of the Grignard reagent or the lithium of the lithiated species may be exchanged for a different metal (i.e. a transmetallation reaction may be performed), for example to zinc (e.g. using $ZnCl_2$) and the intermediate so formed may then be subjected to reaction with a compound of formula IV or V (as appropriate) under conditions known to those skilled in the art, for example such as those described above;

(iii) reaction of a compound of formula VI,



VI

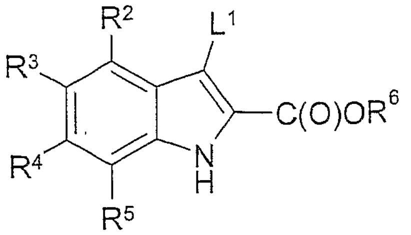
wherein L^3 represents L^1 or L^2 as hereinbefore defined, which group is attached to one or more of the carbon atoms of the benzenoid ring of the indole, and the remaining positions of the benzenoid ring are substituted with 1 to 3 (depending on the number of L^3 substituents) R^2-R^5 substituents, R^2-R^5 represents any one of the substituents, i.e. R^2, R^3, R^4 and R^5, that are already present in that ring (as appropriate), and X, R^1, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a compound of formula VII,

$$R^{17}L^4 \qquad \text{VII}$$

wherein R^{17} represents R^2, R^3, R^4 or R^5 (as appropriate), and L^4 represents L^1 (when L^3 is L^2) or L^2 (when L^3 is L^1) as hereinbefore defined. Such reactions may be performed for example under conditions such as those described hereinbefore in respect of process step (ii) above.

Compounds of formula II may be prepared by:

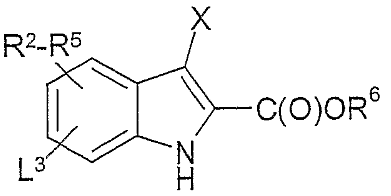
(a) reaction of a compound of formula VIII,



VIII

wherein L^1, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a compound of formula V as hereinbefore defined, for example under conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (ii)) above;

(b) reaction of a compound of formula IX,



IX

wherein X, L^3, R^2-R^5 and R^6 are as hereinbefore defined with a compound of formula VII as hereinbefore defined, for example under conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (iii)) above.

Compounds of formula IV may be prepared by:

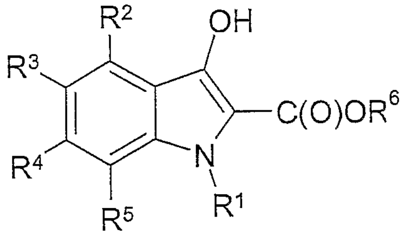
(a) reaction of a compound of formula VIII as hereinbefore defined with a compound of formula X,

R^1L^2 X

wherein R^1 and L^2 are as hereinbefore defined, for example under conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (ii)) above;

(b) reaction of a compound of formula VIII as hereinbefore defined with a compound of formula III as hereinbefore defined, for example under reaction conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (i)); or

(c) for compounds of formula IV wherein L^1 represents a sulfonate group, reaction of a compound of formula XI,



XI

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with an appropriate reagent for the conversion of the hydroxyl group to the sulfonate group (e.g. tosyl chloride, mesyl chloride, triflic anhydride and the like) under conditions known to those skilled in the art.

Compounds of formula VI may be prepared by reaction of a compound of formula IX as hereinbefore defined, with a compound of formula III as hereinbefore defined, for example under reaction conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (i)).

Compounds of formula VI in which L^3 represents L^2 may be prepared by reaction of a compound of formula VI in which L^3 represents L^1, with an appropriate reagent for the conversion of the L^1 group to the L^2 group. This conversion may be performed by methods known to those skilled in the art, for example:

i) compounds of formula VI, in which L^3 is 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl may be prepared by reaction of the reagent bis(pinacolato)diboron with a compound of formula VI in which L^3 represents L^1, for example under reaction conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (ii)) above;

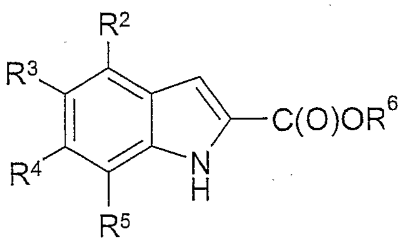
ii) compounds of formula VI, in which L^3 represents $-B(OH)_2$ may be prepared by reaction of a corresponding compound of formula VI in which L^3 represents halo by reaction with, for example, boronic acid or a protected derivative thereof (e.g. bis(pinacolato)diboron or triethyl borate) followed by (if necessary) deprotection under standard conditions. The skilled person will appreciate that the compound of formula VI in which L^3 represents halo may first need to be converted to the corresponding Grignard reagent, or another metal (e.g. *via* a transmetallation reaction), for example under conditions such as those described in respect of preparation of compounds of formula I (process step (ii)) above; or

(iii) compounds of formula VI in which L^3 represents a halo group may be prepared by reaction of a corresponding compound of formula VI in which L^3 represents a different halo group, for example employing a suitable source of halide ions such as those described hereinafter in respect of preparation of compounds of formula VIII (process (a)) under conditions known to those skilled in the art. For example, conversion of a bromo group to an iodo group may be performed in the presence of NaI, optionally in the presence of a suitable catalyst (e.g. CuI) and/or a catalytic amount of base (e.g. *N'N*,-dimethyl-1,2-diaminoethane) in the presence of a suitable solvent such as one described hereinbefore in respect of preparation of compounds of formula I (process step (i)).

Conversions of the L^1, L^4 group and the L^3 group in the compounds of formulae IV, VII and IX, respectively, may be performed in a similar manner to that described above in respect of converting the L^3 group in compounds of formula VI.

Compounds of formula VIII may be prepared by standard techniques. For example:

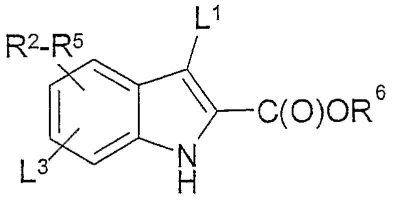
(a) compounds of formula VIII, wherein L^1 represents bromo or iodo, may be prepared by reaction of a compound of formula XII,



XII

wherein R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined, with a reagent, or mixture of reagents known to be a source of bromide or iodide ions (e.g. *N*-bromosuccinimide, iodine, or a mixture of NaI and *N*-chlorosuccinimide). This reaction may be carried out, for example, at room temperature in a suitable solvent (e.g. acetone or benzene);

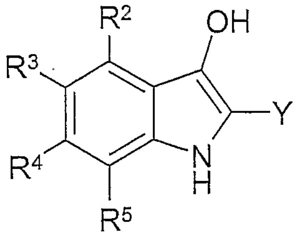
(b) by reaction of a compound of formula XIII,



XIII

wherein L^1, L^3, R^2-R^5 and R^6 are as hereinbefore defined with a compound of formula VII as hereinbefore defined, for example under reaction conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process step (iii)) above; or

(c) compounds of formula VIII, wherein L^1 represents a sulfonate group may be prepared by reaction of a compound of formula XIV,



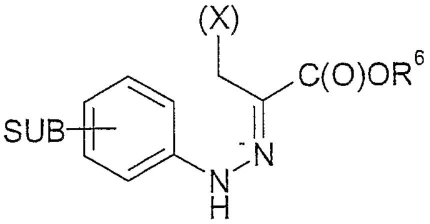
XIV

wherein Y, R^2, R^3, R^4 and R^5 are as hereinbefore defined, with an appropriate reagent for the conversion of the hydroxyl group to a sulfonate group as described hereinbefore.

Compounds of formulae III, V, VII, IX, X, XI, XII, XIII and XIV are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to *inter alia* "*Comprehensive Organic Synthesis*" by B. M. Trost and I. Fleming, Pergamon Press, 1991.

Indoles of formulae II, IV, VI, VIII, IX, XI, XII, XIII and XIV may also be prepared with reference to a standard heterocyclic chemistry textbook (e.g. "*Heterocyclic Chemistry*" by J. A. Joule, K. Mills and G. F. Smith, 3rd edition, published by Chapman & Hall or "*Comprehensive Heterocyclic Chemistry II*" by A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, 1996) and/or made according to the following general procedures.

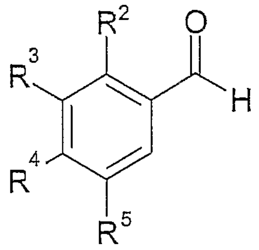
For example, compounds of formulae II, IX and XII may be prepared by reaction of a compound of formula XV,



XV

wherein SUB represents the substitution pattern that is present in the compound of formula II, IX or XII to be formed, (X) either represents the substituent X as hereinbefore defined (as required for formation of compounds of formula II and IX) or hydrogen (as required for formation of compounds of formula XII) and R^6 is as hereinbefore defined, under Fischer indole synthesis conditions known to the person skilled in the art.

Compounds of formula XII may alternatively be prepared by reaction of a compound of formula XVI,



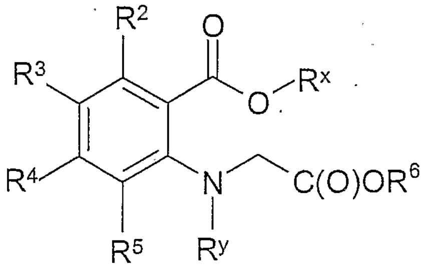
XVI

wherein R^2, R^3, R^4 and R^5 are as hereinbefore defined with a compound of formula XVII,

$$N_3CH_2C(O)OR^6 \qquad \text{XVII}$$

wherein R^6 is as hereinbefore defined, and preferably does not represent hydrogen, under conditions known to the person skilled in the art (i.e. conditions to induce a condensation reaction, followed by a thermally induced cyclisation).

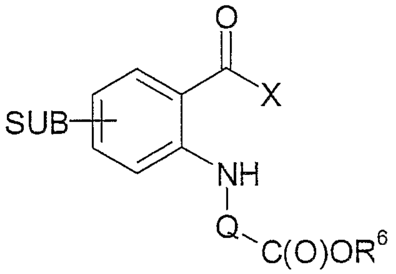
Compounds of formulae XI and XIV may be prepared by reaction of a compound of formula XVIII,



XVIII

wherein R^x represents a C_{1-6} alkyl group, R^y represents either R^1 as hereinbefore defined (as required for formation of compounds of formula XI) or hydrogen (as required for formation of compounds of formula XIV), or a nitrogen-protected derivative thereof, and R^2, R^3, R^4, R^5 and R^6 are as hereinbefore defined for example under cyclisation conditions known to those skilled in the art.

Compounds of formula II and IX may alternatively be prepared by reaction of a compound of formula XIX,

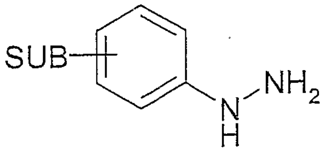


XIX

wherein Q represents either -C(O)- or $-CH_2-$ and SUB, X and R^6 are as hereinbefore defined. When Q represents -C(O)-, the intramolecular cyclisation may be induced by a reducing agent such as $TiCl_3/C_8K$, $TiCl_4/Zn$ or SmI_2 under conditions known to the skilled person, for example, at room temperature in the presence of a polar aprotic solvent (such as THF). When Q represents $-CH_2-$, the reaction may be performed in the presence of base under intramolecular condensation reaction conditions known to the skilled person.

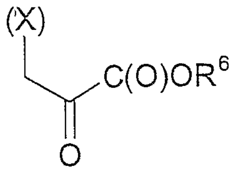
Compounds of formula XV may be prepared by:

(a) reaction of a compound of formula XX,



XX

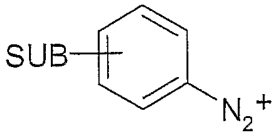
wherein SUB is as hereinbefore defined with a compound of formula XXI,



XXI

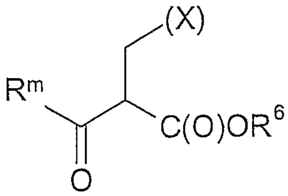
wherein (X) and R^6 are as hereinbefore defined under condensation conditions known to the skilled person; or

(b) reaction of a compound of formula XXII,



XXII

wherein SUB is as hereinbefore defined with a compound of formula XXIII,



XXIII

wherein R^m represents OH, O-C_{1-6} alkyl or C_{1-6} alkyl and (X) and R^6 are as hereinbefore defined, for example under Japp-Klingemann conditions known to the skilled person.

Compounds of formulae XVI, XVII, XVIII, XIX, XX, XXI, XXII and XXIII are either commercially available, are known in the literature, or may be obtained either by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from available starting materials using appropriate reagents and reaction conditions. In this respect, the skilled person may refer to *inter alia* "*Comprehensive Organic Synthesis*" by B. M. Trost and I. Fleming, Pergamon Press, 1991.

The substituents X, R^1, R^2, R^3, R^4, R^5 and R^6 in final compounds of the invention or relevant intermediates may be modified one or more times, after or during the processes described above by way of methods that are well known to those skilled in the art. Examples of such methods include substitutions, reductions, oxidations, alkylations, hydrolyses, esterifications, and etherifications. The precursor groups can be changed to a different such group, or to the groups defined in formula I, at any time during the reaction sequence. For example, in cases where R^6 does not initially represent hydrogen (so providing an ester functional group), the skilled person will appreciate that at any stage during the synthesis (e.g. the final step), the relevant substituent may be hydrolysed to form a carboxylic acid functional group (in which case R^6 will be hydrogen). In this respect, the skilled person may also refer to "*Comprehensive Organic Functional Group Transformations*" by A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, 1995.

Compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

It will be appreciated by those skilled in the art that, in the processes described above and hereinafter, the functional groups of intermediate compounds may need to be protected by protecting groups.

The protection and deprotection of functional groups may take place before or after a reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter. For example, protected compounds/intermediates described herein may be converted chemically to unprotected compounds using standard deprotection techniques.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "*Protective Groups in Organic Chemistry*", edited by J W F McOmie, Plenum Press (1973), and "*Protective Groups in Organic Synthesis*", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

Compounds of the invention are indicated as pharmaceuticals. According to a further aspect of the invention there is provided a compound of the invention for use as a pharmaceutical.

Although compounds of the invention may possess pharmacological activity as such, certain pharmaceutically-acceptable (e.g. "protected") derivatives of compounds of the invention may exist or be prepared which may not possess such activity, but may be administered parenterally or orally and thereafter be metabolised in the body to form compounds of the invention. Such compounds (which may possess some pharmacological activity, provided that such activity is appreciably lower than that of the "active" compounds to which they are metabolised) may therefore be described as "prodrugs" of compounds of the invention.

By "prodrug of a compound of the invention", we include compounds that form a compound of the invention, in an experimentally-detectable amount, within a predetermined time (e.g. about 1 hour), following oral or parenteral administration. All prodrugs of the compounds of the invention are included within the scope of the invention.

Furthermore, certain compounds of the invention (including, but not limited to, compounds of formula I in which R^6 is other than hydrogen) may possess no or minimal pharmacological activity as such, but may be administered parenterally or orally, and thereafter be metabolised in the body to form compounds of the invention that possess pharmacological activity as such (including, but not limited to, corresponding compounds of formula I, in which R^6 represents hydrogen). Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity.

Compounds of the invention are particularly useful because they may inhibit (for example selectively) the activity of prostaglandin E synthases (and particularly microsomal prostaglandin E synthase-1 (mPGES-1)), i.e. they prevent the action of mPGES-1 or a complex of which the mPGES-1 enzyme forms a part, and/or may elicit a mPGES-1 modulating effect, for example as may be demonstrated in the test described below. Compounds of the invention may thus be useful in the treatment of those conditions in which inhibition of a PGES, and particularly mPGES-1, is required.

Compounds of the invention may inhibit the activity of leukotriene C_4 (LTC_4), for example as may be shown in a test such as that described in *Eur. J. Biochem.*, **208**, 725-734 (1992), and may thus be useful in the treatment of those conditions in which inhibition of LTC_4 is required. Compounds of the invention may also inhibit the activity of 5-lipoxygenase-activating protein (FLAP), for example as may be shown in a test such as that described in *Mol. Pharmacol.*, **41**, 873-879 (1992).

Compounds of the invention are thus expected to be useful in the treatment of inflammation.

The term “inflammation” will be understood by those skilled in the art to include any condition characterised by a localised or a systemic protective response, which may be elicited by physical trauma, infection, chronic diseases, such as those mentioned hereinbefore, and/or chemical and/or physiological reactions to external stimuli (e.g. as part of an allergic response). Any such response, which may serve to destroy, dilute or sequester both the injurious agent and the injured tissue, may be manifest by, for example, heat, swelling, pain, redness, dilation of blood vessels and/or increased blood flow, invasion of the affected area by white blood cells, loss of function and/or any other symptoms known to be associated with inflammatory conditions.

The term "inflammation" will thus also be understood to include any inflammatory disease, disorder or condition *per se*, any condition that has an inflammatory component associated with it, and/or any condition characterised by inflammation as a symptom, including *inter alia* acute, chronic, ulcerative, specific, allergic and necrotic inflammation, and other forms of inflammation known to those skilled in the art. The term thus also includes, for the purposes of this invention, inflammatory pain, pain generally and/or fever.

Accordingly, compounds of the invention may be useful in the treatment of inflammatory bowel disease, irritable bowel syndrome, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections (*e.g.* hepatitis C and, particularly, influenza, common cold, herpes zoster, and AIDS), bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies (*e.g.* breast cancer, colon cancer, and prostate cancer), atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, fever (e.g. rheumatic fever), ankylosing spondylitis, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, neurodegenerative disorders such as Alzheimer's disease and multiple sclerosis, autoimmune diseases, osteoporosis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, allergic disorders, rhinitis, ulcers, coronary heart disease, sarcoidosis and any other disease with an inflammatory component. Other diseases that may be mentioned include inflammatory pain, hyperprostaglandin E syndrome, classic Bartter syndrome, Hodgkin's disease and persistent ductus (PDA).

Compounds of the invention may also have effects that are not linked to inflammatory mechanisms, such as in the reduction of bone loss in a subject. Conditions that may be mentioned in this regard include osteoporosis, osteoarthritis, Paget's disease and/or periodontal diseases. Compounds the invention may thus also be useful in increasing bone mineral density, as well as the reduction in incidence and/or healing of fractures, in subjects.

Compounds of the invention are indicated both in the therapeutic and/or prophylactic treatment of the above-mentioned conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a disease which is associated with, and/or which can be modulated by inhibition of LTC_4, FLAP and/or, preferably, a PGES (such as mPGES-1), and/or a method of treatment of a disease in which inhibition of the activity of LTC_4, FLAP and/or, preferably, a PGES (and particularly mPGES-1) is desired and/or required (e.g. inflammation), which method comprises administration of a therapeutically effective amount of a compound of the invention, as hereinbefore defined, to a patient suffering from, or susceptible to, such a condition.

"Patients" include mammalian (including human) patients.

The term "effective amount" refers to an amount of a compound, which confers a therapeutic effect on the treated patient. The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

Compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, sublingually, by any other parenteral route or *via* inhalation, in a pharmaceutically acceptable dosage form.

Compounds of the invention may be administered alone, but are preferably administered by way of known pharmaceutical formulations, including tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like.

Such formulations may be prepared in accordance with standard and/or accepted pharmaceutical practice.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Compounds of the invention may also be combined with other therapeutic agents that are useful in the treatment of inflammation (e.g. NSAIDs and coxibs).

According to a further aspect of the invention, there is provided a combination product comprising:

(A) a compound of the invention, as hereinbefore defined; and

(B) another therapeutic agent that is useful in the treatment of inflammation, wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

Such combination products provide for the administration of a compound of the invention in conjunction with the other therapeutic agent, and may thus be presented either as separate formulations, wherein at least one of those formulations comprises a compound of the invention, and at least one comprises the other therapeutic agent, or may be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including a compound of the invention and the other therapeutic agent).

Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(2) a kit of parts comprising components:

(a) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

Compounds of the invention may be administered at varying doses. Oral, pulmonary and topical dosages may range from between about 0.01 mg/kg of body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day. For e.g. oral administration, the compositions typically contain between about 0.01 mg to about 500 mg, and preferably between about 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily.

In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Compounds of the invention may have the advantage that they are effective, and preferably selective, inhibitors of prostaglandin E synthases (PGES) and particularly microsomal prostaglandin E synthase-1 (mPGES-1). The compounds of the invention may reduce the formation of the specific arachidonic acid metabolite PGE_2 without reducing the formation of other COX generated arachidonic acid metabolites, and thus may not give rise to the associated side-effects mentioned hereinbefore.

Compounds of the invention may also have the advantage that they may be more efficacious than, be less toxic than, be longer acting than, be more potent than, produce fewer side effects than, be more easily absorbed than, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance) than, and/or have other useful pharmacological, physical, or chemical properties over, compounds known in the prior art, whether for use in the above-stated indications or otherwise.

Biological Test

In the assay human mPGES-1 catalyses the reaction where the substrate PGH_2 is converted to PGE_2. mPGES-1 is expressed in *E. coli* and the membrane fraction is dissolved in 20mM NaPi-buffer pH 8.0 and stored at -80 °C. In the assay human mPGES-1 is dissolved in 0.1 M KPi-buffer pH 7.35 with 2.5 mM glutathione. The stop solution consists of H_2O / MeCN (7/3), containing $FeCl_2$ (25 mM) and HCl (0.15 M). The assay is performed at room temperature in 96-well plates. Analysis of the amount of PGE_2 is performed with reversed phase HPLC (Waters 2795 equipped with a 3.9 x 150 mm C18 column). The mobile phase consists of H_2O / MeCN (7/3), containing TFA (0.056%), and absorbance is measured at 195 nm with a Waters 2487 UV-detector.

The following is added chronologically to each well:

1. 100 µL human mPGES-1 in KPi-buffer with glutathione. Total protein concentration: 0.02 mg/mL.
2. 1 µL inhibitor in DMSO. Incubation of the plate at room temperature for 25 minutes.
3. 4 µL of a 0.25 mM PGH_2 solution. Incubation of the plate at room temperature for 60 seconds.
4. 100 µL stop solution.

180 µL per sample is analyzed with HPLC.

Examples

The invention is illustrated by way of the following examples, in which the following abbreviations may be employed:

cy	cyclohexyl
dba	dibenzylideneacetone
DIBAL	diisobutylaluminium hydride
DMAP	4,4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
HPLC	High Pressure Liquid Chromatography
MeCN	acetonitrile
MS	mass spectrum
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
THF	tetrahydrofuran
xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)-xanthene

Starting materials and chemical reagents specified in the syntheses described below are commercially available from, *e.g.* Sigma-Aldrich Fine Chemicals.

Example 1

5-(4-*tert*-Butylphenyl)-1,3-bis(4-isopropoxyphenyl)-indole-2-carboxylic acid

(a) 5-(4-*tert*-Butylphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-bromoindole-2-carboxylic acid ethyl ester (3.48 g, 13 mmol), 4-*tert*-butylphenylboronic acid (4.63 g, 26 mmol), K_3PO_4 (9.93 g, 45 mmol), $Pd(OAc)_2$ (146 mg, 0.65 mmol), tri-*o*-tolylphosphine (396 mg, 1.3 mmol), EtOH (20 ml) and toluene (10 mL) was stirred under argon for 20 min at room temperature, and then heated at 100°C for 24 h. The mixture was allowed to cool, poured into $NaHCO_3$ (aq., sat.) and extracted with EtOAc. The combined extracts were washed with water and brine and then dried over Na_2SO_4. Concentration and purification by chromatography gave the sub-title compound (3.27 g, 78%).

(b) 5-(4-*tert*-Butylphenyl)-3-iodoindole-2-carboxylic acid ethyl ester

This reaction was performed with the exclusion of light. A solution of NaI (300mg, 2.0 mmol) in acetone (15 mL) was added dropwise to a stirred solution of *N*-chlorosuccinimide (270 mg, 2.0 mmol) in acetone (4 mL), followed, after 15 min, by the dropwise addition of 5-(4-*tert*-butylphenyl)indole-2-carboxylic acid ethyl ester (650mg, 2.0 mmol; see step (a) above) in acetone (20 mL). After 30 min at room temperature the mixture was poured into $Na_2S_2O_3$ (aq., 10%, 40 mL) and extracted with EtOAc. The combined extracts were washed with water and brine and then dried over Na_2SO_4. The organic phase was then concentrated and purified by chromatography to give the sub-title compound. This product was employed in the subsequent steps without further purification.

(c) 5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester

5-(4-*tert*-Butylphenyl)-3-iodoindole-2-carboxylic acid ethyl ester (146 mg, 0.32 mmol; see step (b) above), 4-isopropoxyphenylboronic acid (86 mg, 0.48 mmol), K_3PO_4 (238 mg, 1.12 mmol), $Pd(OAc)_2$ (3.6 mg, 0.016 mmol) and toluene (3 mL) was stirred for 20 min at room temperature and for 4 h at 80°C. The mixture was poured into $NaHCO_3$ (aq., sat.) and extracted with EtOAc. The combined extracts were washed with water and brine and then dried over Na_2SO_4. Concentration and purification by column chromatography gave the sub-title compound.

(d) 5-(4-*tert*-Butylphenyl)-1,3-bis(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester

Anhydrous CH_2Cl_2 (15 mL), followed by triethylamine (490 µL, 352 mg, 3.48 mmol), pyridine (280 µL, 275 mg, 3.48 mmol) and 3Å molecular sieves (ca. 2 g) were added to 5-(4-*tert*-butylphenyl)-3-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (793 mg, 1.74 mmol; see step (c) above), $Cu(OAc)_2$ (632 mg, 3.48 mmol), and 4-isopropoxyphenylboronic acid (626 mg, 3.48 mmol). The mixture was stirred vigorously at ambient temperature for 30 h and was then filtered through Celite®. The filter cake was washed with EtOAc, concentrated and purified by chromatography to afford the sub-title compound.

(e) 5-(4-*tert*-Butylphenyl)-1,3-bis(4-isopropoxyphenyl)-indole-2-carboxylic acid

A mixture of 5-(4-*tert*-butylphenyl)-1,3-bis(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (166 mg, 0.281 mmol; see step (d) above), aqueous NaOH (1M, 10 mL) and MeCN (40 mL) was heated at reflux for 4 h, allowed to cool, acidified with 1M HCl to pH 2 and extracted with EtOAc. The combined extracts were washed with water and brine and then dried over Na_2SO_4. Concentration, purification by chromatography, and successive recrystallisations from EtOH and then MeCN gave the title compound.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 13.1-12.5 (1H, br s), 7.69 (1H, s), 7.59-7.37 (7H, m), 7.36-7.25 (2H, m), 7.19-7.11 (1H, m), 7.10-6.94 (4H, m), 4.67 (1H, septet, J=6.1 Hz), 4.65 (1H, septet J=6.1 Hz), 1.31 (6H, d, J=6.1 Hz), 1.30 (6H, d, J=6.1 Hz), 1.27 (9H, s).

Example 2

5-(4-*tert*-Butylphenyl)-1-(3-isopropoxyphenyl)-3-(4-isopropoxyphenyl)-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid, and 3-isopropoxyphenylboronic acid.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 12.9-12.8 (1H, br s), 7.72-7.70 (1H, m), 7.62-7.35 (8H, m), 7.30-7.21 (1H, m), 7.07-6.90 (5H, m), 4.77-4.55 (2H, m), 1.38-1.23 (21H, m).

Example 3

5-(4-*tert*-Butylphenyl)-1-(2-isopropoxyphenyl)-3-(4-isopropoxyphenyl)-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid and 2-isopropoxyphenylboronic acid.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 12.5-12.4 (1H, br s), 7.65 (1H, s), 7.58-7.33 (9H, m), 7.24-6.93 (5H, m), 4.66 (1H, septet, J=6.0 Hz), 4.46 (1H, septet, J=6.0 Hz), 1.31 (6H, d, J=6.0 Hz), 1.28 (9H, s), 1.10 (3H, d, J=6.0 Hz), 1.02 (3H, d, J=6.0 Hz).

Example 4
5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(5-(trifluoromethyl)-pyrid-2-yl)indole-2-carboxylic acid

(a) 5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(5-(trifluoromethyl)-pyrid-2-yl)indole-2-carboxylic acid ethyl ester

CuI (7.6 mg, 40 nmol), *N,N'*-dimethyl-1,2-diaminoethane (13 µL, 120 nmol) and toluene (0.5 mL) were added to a mixture of 5-(4-*tert*-butylphenyl)-3-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (182 mg, 400 nmol; see Example 1(c)), 2-bromo-5-(trifluoromethyl)pyridine (181 mg, 800 mmol), K_3PO_4 (196 mg, 800 nmol) and toluene (2 mL) under argon. The mixture was heated at 110°C for 27 h. Additional portions of CuI (7.6 mg, 40 nmol) and *N,N'*-dimethyl-1,2-diaminoethane (13 µL, 120 nmol) were added and the heating was continued for a further 22 h. The mixture was filtered through Celite® and the filter cake was washed with EtOAc. The filtrate was concentrated and purified by chromatography to give the sub-title compound (66 mg, 28%).

(b) 5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(5-(trifluoromethyl)-pyrid-2-yl)indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 5-(4-*tert*-butylphenyl)-3-(4-isopropoxyphenyl)-1-(5-(trifluoromethyl)pyrid-2-yl)indole-2-carboxylic acid ethyl ester (see step (a) above) in accordance with the procedure described in Example 1(e).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 13.2-13.0 (1H, br s), 9.03 (1H, s), 8.47 (1H, dd, J=8.6, 2.2 Hz), 7.90 (1H, d, J=8.6 Hz), 7.75-7.65 (3H, m), 7.60-7.40 (6H, m), 7.09-6.98 (2H, m), 4.68 (1H, septet, J=6.0 Hz), 1.31 (6H, d, J=6.0 Hz), 1.28 (9H, s).

Example 5

5-(4-*tert*-Butylphenyl)-1-(4-(dimethylamino)phenyl)-3-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 4, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid, and 1-bromo-4-(dimethylamino)benzene.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 12.9-12.8 (1H, br s), 7.78 (1H, s), 7.66-7.45 (7H, m), 7.35-7.19 (3H, m), 7.14-7.02 (2H, m), 6.99-6.85 (2H, m), 4.74 (1H, septet, J=6.0 Hz), 3.06 (6H, s), 1.39 (6H, d, J=6.0 Hz), 1.37 (9H, s).

Example 6

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(4-(isopropylamino)-phenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 4, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid, and 1-bromo-4-(isopropylamino)-benzene.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 7.70 (1H, s), 7.62-7.36 (7H, m), 7.19-7.05 (3H, m), 7.04-6.92 (2H, m), 6.70-6.58 (2H, m), 5.8-5.6 (1H, br s), 4.65 (1H, septet, J=6.1 Hz), 3.65-3.47 (1H, m), 1.30 (6H, d, J=6.1 Hz), 1.28 (9H, s), 1.17 (6H, d, J=6.3 Hz).

Example 6A

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(4-(isopropylamino)-phenyl)indole-2-carboxylic acid hydrochloride

4M HCl in dioxane (1.5 eq.) was added to 5-(4-*tert*-butylphenyl)-3-(4-isopropoxyphenyl)-1-(4-(isopropylamino)phenyl)indole-2-carboxylic acid (0.1 mmol/mL; see Example 6) in anhydrous Et_2O. The solvent was removed under reduced pressure and the residue triturated with anhydrous Et_2O. The solid was collected by filtration and dried *in vacuo*.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 7.69 (1H, s), 7.64-6.94 (14H, m), 4.66 (1H, septet, J=6.1 Hz), 3.54-3.55 (1H, m), 1.30 (6H, d, J=6.1 Hz), 1.28 (9H, s), 1.22 (6H, d, J=6.3 Hz).

Example 7

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(6-isopropoxypyrid-3-yl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 4, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid, and 5-bromo-2-isopropoxypyridine.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 13.0-12.8 (1H, br s), 8.23 (1H, d, J=2.7 Hz), 7.79 (1H, dd, J=8.7, 2.7 Hz), 7.68 (1H, s), 7.58-7.37 (7H, m), 7.14 (1H, d, J=8.7 Hz), 7.04-6.94 (2H, m), 6.89 (1H, d, J=8.8 Hz), 5.25 (1H, septet, J=6.2 Hz), 4.65 (1H, septet, J=6.0 Hz), 1.34 (6H, d, J=6.2 Hz), 1.30 (6H, d, J=6.0 Hz), 1.28 (9H, s).

Example 7A

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(6-isopropoxypyrid-3-yl)indole-2-carboxylic acid hydrochloride

The title compound was prepared in accordance with Example 6A from 5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(6-isopropoxypyrid-3-yl)-indole-2-carboxylic acid (see Example 7).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.23 (1H, d, J=2.7 Hz), 7.79 (1H, dd, J=8.7, 2.7 Hz), 7.67 (1H, s), 7.62-7.34 (7H, m), 7.15 (1H, d, J=8.7 Hz), 7.05-6.96 (2H, m), 6.91 (1H, d, J=8.7 Hz), 5.30 (1H, septet, J=6.2 Hz), 4.66 (1H, septet, J=6.0 Hz), 1.34 (6H, d, J=6.2 Hz), 1.30 (6H, d, J=6.0 Hz), 1.28 (9H, s).

Example 8

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 4, using 5-bromoindole-2-carboxylic acid ethyl ester, 4-*tert*-butylphenylboronic acid, 4-isopropoxyphenylboronic acid, and 4-bromo-1-methyl-2-nitrobenzene.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 13.0 (1H, br s), 8.10 (1H, d, J=2.0 Hz), 7.76 (1H, dd, J=8.2, 2.0 Hz), 7.72-7.65 (2H, m), 7.61 (1H, dd, J=8.7, 1.4 Hz), 7.56-7.38 (6H, m), 7.25 (1H, d, J=8.7 Hz), 7.06-6.96 (2H, m), 4.67 (1H, septet, J=6.0 Hz) 2.61 (3H, s) 1.31 (6H, d, J=6.0 Hz) 1.30 (9H, s).

Example 9

3,6-Bis(4-isopropoxyphenyl)-1-(naphthalen-2-yl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1, using 6-bromoindole-2-carboxylic acid ethyl ester, 4-isopropoxyphenylboronic acid, and naphthalen-2-ylboronic acid.

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.12-7.95 (4H, m), 7.70-7.36 (9H, m), 7.33-7.28 (1H, m), 7.05-6.84 (4H, m), 4.64 (1H, septet, J= 6.0 Hz), 4.56 (1H, septet, J= 6.0 Hz), 1.30 (6H, d, J=6.0 Hz), 1.22 (6H, d, J=6.0 Hz).

Example 9A

Sodium 3,6-bis(4-isopropoxyphenyl)-1-(naphthalen-2-yl)indole-2-carboxylate

To a solution of 3,6-bis(4-isopropoxyphenyl)-1-(naphthalen-2-yl)-indole-2-carboxylic acid (37 mg, 67 nmol) in CH_2Cl_2 was added a stock solution of MeONa (3.37 M, 19.9 μL). The mixture was stirred at room temperature for 20 min. The precipitate was collected by filtration and dried *in vacuo* to afford the title compound (25 mg, 65%).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.12-7.95 (4H, m), 7.76-7.65 (4H, m), 7.62-7.61 (6H, m), 7.00-6.87 (4H, m), 4.63 (1H, septet, J= 6.0 Hz), 4.57 (1H, septet, J= 6.0 Hz), 1.31 (6H, d, J=6.0 Hz), 1.25 (6H, d, J=6.0 Hz).

Example 10

1,3,6-Tris(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1, using 6-bromoindole-2-carboxylic acid ethyl ester, and 4-isopropoxyphenylboronic.

Example 10A

Sodium 1,3,6-tris(4-isopropoxyphenyl)-indole-2-carboxylate

The title compound was prepared in accordance with Example 9A from 1,3,6-tris(4-isopropoxyphenyl)indole-2-carboxylic acid (see Example 10). 200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 7.71-5.59 (3H, m), 7.53-7.39 (4H, m), 7.32-7.27 (1H, m), 7.23-7.22 (1H, m), 7.06-6.89 (6H, m), 4.73-4.54 (3H, m), 1.35-1.23 (18H, m).

Example 11

1-(6-Isopropoxypyrid-3-yl)-3-(pyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)-indole-2-carboxylic acid

(a) 3-Iodo-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1(a) and 1(b), using 5-bromoindole-2-carboxylic acid ethyl ester, 4-(trifluoromethyl)phenylboronic acid, NaI and *N*-chlorosuccinimide.

(b) 3-(Pyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester

$Pd(PCy_3)_2$ (0.055 mmol, 5.5 mL, 5 mol%) in dioxane was added to a stirred mixture of 3-iodo-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (480 mg, 1.1 mmol; see step (a)), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (248 mg, 1.21 mmol), Na_2CO_3 (aq. 2M, 2.75 µL, 5.5 mmol) and dioxane (13 mL) at room temperature. The mixture was stirred at 80°C for 16 h, allowed to cool, diluted with EtOAc and then washed with brine, dried over $MgSO_4$, concentrated and purified by chromatography to yield the sub-title compound (376 mg, 79%).

(c) <u>5-Bromo-2-isopropoxypyridine</u>

$AgCO_3$ (1.3 g, 5 mmol), toluene (15 mL) and 2-iodopropane (1.2 mL, 12 mmol) were added to 5-bromopyridin-2(1*H*)-one (1.74 g, 10 mmol). The mixture was stirred at 50 °C for 16 h, after which it was allowed to cool, then diluted with EtOAc and filtered through Celite®. The filter cake was washed with EtOAc and the combined filtrates concentrated and purified by distillation to yield the sub-title compound (1.12 g, 52%).

(d) <u>1-(6-Isopropoxypyrid-3-yl)-3-(pyrid-3-yl)-5-(4-(trifluoromethyl)-phenyl)indole-2-carboxylic acid ethyl ester</u>

A mixture of CuI (7.6 mg, 40 nmol) and *N,N'*-dimethyl-1,2-diaminoethane (13 µL, 120 nmol) in toluene (0.5 mL) was added to a stirred mixture of 3-(pyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (164 mg, 400 nmol; see step (b)), 5-bromo-2-isopropoxypyridine (216 mg, 1 mmol; see step (c)), K_3PO_4 (196 mg, 800 nmol) and toluene (2 mL) at room temperature under argon. The mixture was stirred at 110 °C for 5 h and at 140 °C for 16 h, after which it was allowed to cool and filtered through Celite®. The filter cake was washed with EtOAc and the combined filtrates concentrated and purified by chromatography to yield the sub-title compound (57 mg, 29%).

(e) 1-(6-Isopropoxypyrid-3-yl)-3-(pyrid-3-yl)-5-(4-(trifluoromethyl)-phenyl)indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 1-(6-isopropoxypyrid-3-yl)-3-(pyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (see step (d)) in accordance with the procedure described in Example 1(e).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.90-8.71 (1H, m), 8.65-8.43 (1H, m), 8.26 (1H, d, J=2.6 Hz), 8.10-7.99 (1H, m), 7.94-7.71 (6H, m), 7.66 (1H, d, J=8.8 Hz), 7.56-7.41 (1H, m), 7.23 (1H, d, J=8.8 Hz), 6.91 (1H, d, J=8.8 Hz), 5.30 (1H, septet, J=6.0 Hz), 1.34 (6H, d, J=6.0 Hz).

Example 12

3-(6-Isopropoxypyrid-3-yl)-1-(4-(trifluoromethoxy)phenyl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid

(a) 2-Isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

A mixture of 5-bromo-2-isopropoxypyridine (300 mg, 1.4 mmol; see Example 11(c)), KOAc (206 mg, 1.54 mmol) and bispinacolatodiborane (391 mg, 1.54 mmol) in dioxane (10 mL) was stirred under argon at 80 °C. A mixture of $Pd_2(dba)_3$ (46 mg, 50 nmol), PCy_3 (84 mg, 300 nmol) and anhydrous dioxane (5 mL) was added. The combined mixture was stirred at 80 °C for 16 h, after which it was allowed to cool and filtered through Celite®. The filter cake was washed with EtOAc and the combined filtrates concentrated and purified by chromatography to yield the sub-title compound (216 mg, 59%).

(b) 3-(6-Isopropoxypyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester

A mixture of $Pd_2(dba)_3$ (23 mg, 25 nmol) and PCy_3 (42 mg, 150 nmol) in anhydrous dioxane (5 mL) was stirred and then added to a mixture of 3-

iodo-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (326 mg, 0.71 mmol; see Example 11(a)), 2-isopropoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (205 mg, 0.78 mmol; see step (a) above), Na_2CO_3 (aq. 2M, 1.17 mL, 2.34 mmol) and dioxane under argon at 80 °C. The mixture was stirred at 80 °C for 16 h, after which it was allowed to cool and extracted with EtOAc. The combined extracts were washed with brine, dried over $MgSO_4$, concentrated and purified by chromatography to yield the sub-title compound (219 mg, 66%).

(c) 3-(6-Isopropoxypyrid-3-yl)-1-(4-(trifluoromethoxy)phenyl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with the procedure described in Example 1(d) from 3-(6-isopropoxypyrid-3-yl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (see step (b)) and 4-(trifluoromethoxy)phenylboronic acid.

(d) 3-(6-Isopropoxypyrid-3-yl)-1-(4-(trifluoromethoxy)phenyl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid

The title compound was prepared by hydrolysis of 3-(6-isopropoxypyrid-3-yl)-1-(4-(trifluoromethoxy)phenyl)-5-(4-(trifluoromethyl)phenyl)indole-2-carboxylic acid ethyl ester (see step (c)) in accordance with the procedure described in Example 1 (e).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.46-8.33 (1H, m), 7.98-7.71 (6H, m), 7.68-7.51 (5H, m), 7.26 (1H, d, J=8.8 Hz), 6.87-6.79 (1H, m), 5.30 (1H, septet, J=5.9 Hz), 1.32 (6H, d, J=5.9 Hz).

Example 13

5-(4-*tert*-Butylphenyl)-3-(4-isopropoxyphenyl)-1-pyrid-3-yl-1H-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1(d) from 5-(4-*tert*-butylphenyl)-3-(4-*iso*-propoxyphenyl)-1*H*-indole-2-carboxylic acid ethyl ester (see Example 1(c)) and 3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridine, followed by ester hydrolysis in accordance with the procedure described in Example 1(e).

200 MHz ^{1}H-NMR (DMSO-d_6, ppm) δ 8.72-8.52 (2H, m) 8.01-7.91 (1H, m) 7.72-7.38 (9H, m) 7.17 (1H, d, J=8.4 Hz) 7.07-6.95 (2H, m) 4.70 (1H, septet, J=6.1 Hz) 1.31 (6H, d, J=6.1 Hz) 1.28 (9H, s).

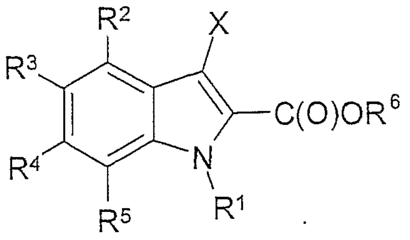
Example 14

Title compounds of the examples were tested in the biological test described above and were found to exhibit 50% inhibition of mPGES-1 at a concentration of 10 μM or below. For example, for the following compounds of the examples, 50% inhibition was observed at:

Example 2:	350 nM
Example 5:	210 nM
Example 6:	70 nM
Example 11:	1800 nM
Example 13:	950 nM

Claims

1. A compound of formula I,



I

wherein

X and R^1 independently represent an aryl group or a heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from A;

one of the groups R^2, R^3, R^4 and R^5 represents an aryl group or a heteroaryl group (both of which are optionally substituted by one or more substituents selected from A) and:

a) the other groups are independently selected from hydrogen, G^1, an aryl group, a heteroaryl group (which latter two groups are optionally substituted by one or more substituents selected from A), C_{1-8} alkyl and a heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from G^1 and/or Z^1); and/or

b) any two other groups which are adjacent to each other are optionally linked to form, along with two atoms of the essential benzene ring in the compound of formula I, a 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^6$, $-OR^6$ and $=O$;

A represents, on each occasion when mentioned above:

I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B;

II) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^1 and/or Z^1;

III) a G^1 group; or

IV) two A substituents may be linked together to form, along with at least two (e.g. adjacent) atoms of the aryl or heteroaryl group to which the two A substituents are attached, a further 3- to 5-membered ring, which ring optionally contains 1 to 3 hetereoatoms and/or 1 to 2 double bonds, and which is optionally substituted by halo or C_{1-8} alkyl, which latter group is optionally substituted by halo;

R^6 represents, on each occasion when mentioned above:

I) hydrogen;

II) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B; or

III) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^1 and/or Z^1;

G^1 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^7$;

wherein A^1 represents a single bond or a spacer group selected from $-C(O)A^2-$, $-S(O)_nA^3-$, $-N(R^8)A^4-$ or $-OA^5-$, in which:

A^2 and A^3 independently represent a single bond, -O-, $-N(R^8)-$ or -C(O)-;

A^4 and A^5 independently represent a single bond, -C(O)-, $-C(O)N(R^8)-$, -C(O)O-, $-S(O)_n-$ or $-S(O)_nN(R^8)-$;

Z^1 represents, on each occasion when mentioned above, =O, =S, $=NOR^7$, $=NS(O)_nN(R^8)(R^7)$, =NCN or $=C(H)NO_2$;

B represents, on each occasion when mentioned above:

I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^2, methylenedioxy, difluoromethylenedioxy and/or dimethylmethylenedioxy;

II) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G^2 and/or Z^2;

III) a G^2 group; or

IV) methylenedioxy, difluoromethylenedioxy or dimethylmethylenedioxy;

G^2 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^6-R^9$;

wherein A^6 represents a single bond or a spacer group selected from $-C(O)A^7-$, $-S(O)_nA^8-$, $-N(R^{10})A^9-$ or $-OA^{10}-$, in which:

A^7 and A^8 independently represent a single bond, -O-, $-N(R^{10})-$ or -C(O)-;

A^9 and A^{10} independently represent a single bond, -C(O)-, $-C(O)N(R^{10})-$, -C(O)O-, $-S(O)_n-$ or $-S(O)_nN(R^{10})-$;

Z^2 represents, on each occasion when mentioned above, =O, =S, $=NOR^9$, $=NS(O)_nN(R^{10})(R^9)$, =NCN or $=C(H)NO_2$;

R^7, R^8, R^9 and R^{10} are independently selected from:

i) hydrogen;

ii) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^3, methylenedioxy, difluoromethylenedioxy and/or dimethylmethylenedioxy;

iii) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by G^3 and/or Z^3; or

any pair of R^7 and R^8, or R^9 and R^{10}, may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms a further 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from G^3 and/or Z^3;

G^3 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{11}-R^{11}$;

wherein A^{11} represents a single bond or a spacer group selected from $-C(O)A^{12}-$, $-S(O)_nA^{13}-$, $-N(R^{12})A^{14}-$ or $-OA^{15}-$, in which:

A^{12} and A^{13} independently represent a single bond, $-O-$, $-N(R^{12})-$ or $-C(O)-$;

A^{14} and A^{15} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{12})-$, $-C(O)O-$, $-S(O)_n-$ or $-S(O)_nN(R^{12})-$;

Z^3 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{11}$, $=NS(O)_nN(R^{12})(R^{11})$, $=NCN$ or $=C(H)NO_2$;

n represents, on each occasion when mentioned above, 1 or 2;

R^{11} and R^{12} are independently selected from:

i) hydrogen;

ii) C_{1-6} alkyl or a heterocycloalkyl group, both of which groups are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$, $-O(R^{13})$ and $=O$; and

iii) an aryl or heteroaryl group, both of which are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$ and $-O(R^{13})$; or any pair R^{11} and R^{12} may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms a further 3- to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{13})(R^{14})$, $-O(R^{13})$ and $=O$;

R^{13} and R^{14} are independently selected from hydrogen and C_{1-4} alkyl, which latter group is optionally substituted by one or more halo groups;

or a pharmaceutically-acceptable salt thereof.

2. A compound as claimed in Claim 1, wherein:
A^2 and A^3 independently represent a single bond, -O- or $-N(R^8)-$;
Z^1 represents, on each occasion when mentioned above, $=O$, $=NOR^7$, $=NS(O)_nN(R^8)(R^7)$, $=NCN$ or $=C(H)NO_2$;
A^7 and A^8 independently represent a single bond, -O- or $-N(R^{10})-$;
Z^2 represents, on each occasion when mentioned above, $=O$, $=NOR^9$, $=NS(O)_nN(R^{10})(R^9)$, $=NCN$ or $=C(H)NO_2$;
A^{12} and A^{13} independently represent a single bond, -O- or $-N(R^{12})-$; and/or
Z^3 represents, on each occasion when mentioned above, $=O$, $=NOR^{11}$, $=NS(O)_nN(R^{12})(R^{11})$, $=NCN$ or $=C(H)NO_2$.

3. A compound as claimed in Claim 1 or Claim 2, wherein n represents 2.

4. A compound as claimed in any one of the preceding claims, wherein A represents G^1.

5. A compound as claimed in any one of the preceding claims, wherein G^1 represents halo, cyano, $-NO_2$ or $-A^1-R^7$.

6. A compound as claimed in Claim 5, wherein G^1 represents $-NO_2$ or $-A^1-R^7$.

7. A compound as claimed in any one of the preceding claims, wherein A^1 represents a single bond, $-N(R^8)A^4-$ or $-OA^5-$.

8. A compound as claimed in any one of the preceding claims, wherein A^4 and A^5 independently represent a single bond.

9. A compound as claimed in any one of the preceding claims, wherein R^7 and R^8 are independently selected from hydrogen and C_{1-6} alkyl, which latter group is optionally substituted by one or more substituents selected from G^3.

10. A compound as claimed in any one of the preceding claims, wherein G^3 represents halo.

11. A compound as claimed in any one of the preceding claims, wherein R^1 represents an optionally substituted phenyl, naphthyl or pyridyl group.

12. A compound as claimed in any one of the preceding claims, wherein X represents an optionally substituted phenyl or pyridyl group.

13. A compound as claimed in any one of the preceding claims, wherein R^3 and R^4 independently represent G^1, hydrogen or an optionally substituted phenyl or pyridyl group.

14. A compound as claimed in Claim 13, wherein R^3 and R^4 independently represent hydrogen or an optionally substituted phenyl or pyridyl group.

15. A compound as claimed in any one of the preceding claims, wherein at least one of R^3 and R^4 represents optionally substituted phenyl or pyridyl, and up to one other represents G^1 or hydrogen.

16. A compound as claimed in any one of Claims 13 to 15, wherein when R^3 or R^4 represents an optionally substituted phenyl or pyridyl group, then the other substituents on the essential benzene ring of the indole of formula I, as defined in Claim 1, (i.e. R^2, R^5 and R^3 or R^4 (as appropriate)) independently represent G^1 or hydrogen.

17. A compound as claimed in Claim 16, wherein the other substituents represent hydrogen.

18. A compound as claimed in any one of Claims 11 to 17, wherein the optional substituents are selected from cyano, heterocycloalkyl, halo, $-NO_2$, C_{1-6} alkyl (which alkyl group may be linear or branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more halo group), $-OR^{15}$ and $-N(R^{15})R^{16}$, wherein R^{15} and R^{16} independently represent, H or C_{1-6} alkyl (which alkyl group is optionally substituted by one or more halo groups)

19. A compound as claimed in Claim 18, wherein the optional substituents are selected from halo, $-NO_2$, C_{1-6} alkyl (which alkyl group may be linear or branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more halo group), $-OR^{15}$ and $-N(R^{15})R^{16}$, wherein

R^{15} and R^{16} independently represent, H or C_{1-6} alkyl (which alkyl group is optionally substituted by one or more halo groups).

20. A compound as claimed in any one of the preceding claims, wherein R^6 represents hydrogen.

21. A compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, for use as a pharmaceutical.

22. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

23. The use of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease in which inhibition of the activity of microsomal prostaglandin E synthase-1, leukotriene C_4 and/or 5-lipoxygenase-activaing protein is desired and/or required.

24. A use as claimed in Claim 23, wherein inhibition of the activity of microsomal prostaglandin E synthase-1 is desired and/or required.

25. A use as claimed in Claim 23 or Claim 24, wherein the disease is inflammation.

26. A use as claimed in Claim 25 wherein the disease is inflammatory bowel disease, irritable bowel syndrome, migraine, headache, low back pain, fibromyalgia, a myofascial disorder, a viral infection, a bacterial infection, a fungal infection, dysmenorrhea, a burn, a surgical or dental procedure, a malignancy, atherosclerosis, gout, arthritis, osteoarthritis,

juvenile arthritis, rheumatoid arthritis, fever, ankylosing spondylitis, systemic lupus erythematosus, vasculitis, pancreatitis, nephritis, bursitis, conjunctivitis, iritis, scleritis, uveitis, wound healing, dermatitis, eczema, psoriasis, stroke, diabetes mellitus, a neurodegenerative disorder, an autoimmune disease, osteoporosis, asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, an allergic disorder, rhinitis, an ulcer, coronary heart disease, sarcoidosis, inflammatory pain, hyperprostaglandin E syndrome, classic Bartter syndrome, Hodgkin's disease, persistent ductus, any other disease with an inflammatory component, Paget's disease or a periodontal disease.

27. A method of treatment of a disease in which inhibition of the activity of mPGES-1, LTC_4 and/or FLAP is desired and/or required, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

28. A method as claimed in Claim 27, wherein inhibition of the activity of mPGES-1 is desired and/or required.

29. A combination product comprising:
(A) a compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof; and
(B) another therapeutic agent that is useful in the treatment of inflammation,
wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

30. A combination product as claimed in Claim 29 which comprises a pharmaceutical formulation including a compound as defined in any one of

Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

31. A combination product as claimed in Claim 29 which comprises a kit of parts comprising components:

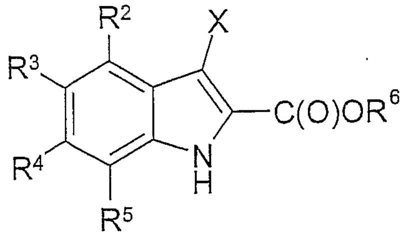
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 20, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

32. A process for the preparation of a compound as defined in Claim 1, which comprises:

(i) reaction of a compound of formula II,



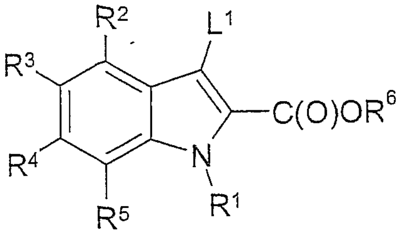
II

wherein X, R^2, R^3, R^4, R^5 and R^6 are as defined in Claim 1, with a compound of formula III,

R^1L^1 III

wherein L^1 represents a suitable leaving group and R^1 is as defined in Claim 1;

(ii) reaction of a compound of formula IV,



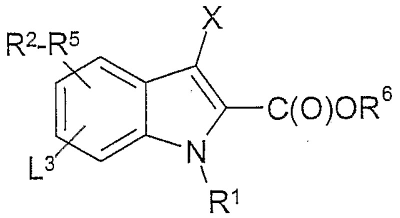
IV

wherein L^1 is as defined above and R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Claim 1, with a compound of formula V,

$$XL^2 \qquad V$$

wherein L^2 represents a suitable leaving group and X is as defined in Claim 1;

(iii) reaction of a compound of formula VI,



VI

wherein L^3 represents L^1 or L^2 as defined above, which group is attached to one or more of the carbon atoms of the benzenoid ring of the indole, and the remaining positions of the benzenoid ring are substituted with 1 to 3 (depending on the number of L^3 substituents) R^2-R^5 substituents, R^2-R^5 represents any one of the substituents, i.e. R^2, R^3, R^4 and R^5, that are already present in that ring (as appropriate), and X, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in Claim 1, with a compound of formula VII,

$$R^{17}L^4 \qquad VII$$

wherein R^{17} represents R^2, R^3, R^4 or R^5 (as appropriate), and L^4 represents L^1 (when L^3 is L^2) or L^2 (when L^3 is L^1) as defined above.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2005/002404

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/42 C07D401/04 C07D401/14 A61K31/404 A61P29/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/46195 A (FAULL ALAN WELLINGTON ; KETTLE JASON (GB); ASTRAZENECA UK LTD (GB)) 10 August 2000 (2000-08-10) claims	1,22,23, 27,29,32

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention *cannot be considered novel or cannot be considered* to involve an inventive step when the document is taken alone

"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 17 October 2005	Date of mailing of the international search report 21/10/2005
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Diederen, J

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/002404

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27,28 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[redacted]onal Application No
PCT/GB2005/002404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0046195 A	10-08-2000	AT 235465 T	15-04-2003
		AU 2120900 A	25-08-2000
		DE 60001811 D1	30-04-2003
		DE 60001811 T2	24-12-2003
		EP 1159269 A1	05-12-2001
		JP 2003502279 T	21-01-2003
		US 6911465 B1	28-06-2005