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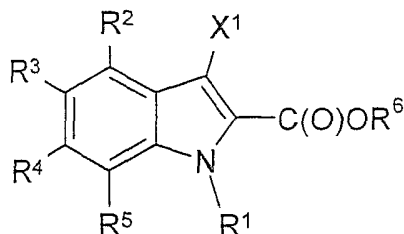
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(54) Title: INDOLES USEFUL IN THE TREATMENT OF INFLAMMATION



(I)

(57) Abstract: There is provided compounds of formula (I), Wherein X^1 , 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 a member of the MAPEG family is desired and/or required, and particularly in the treatment of inflammation.

INDOLES USEFUL IN THE TREATMENT OF INFLAMMATION

Field of the Invention

5 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 C₄
10 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.

15

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
20 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
25 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 cardiovascular diseases are known to have
30 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 β -agonists which affect the bronchoconstriction element, whereas patients with
5 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
10 (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
15 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
20 (PGH_2). PGH_2 is further metabolized 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
25 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
30 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 C₄, D₄ and E₄ (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 CysLT₁ and CysLT₂. 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 CysLT₁. 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 C₄ synthase may be mentioned. A FLAP inhibitor would also decrease the formation of the proinflammatory LTB₄.

mPGES-1, FLAP and leukotriene C₄ 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 PGE₂, 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

Indole-based compounds have been disclosed in international patent applications WO 96/03377, WO 01/00197, WO 03/044014 and WO 03/057670, US patents Nos. 5,189,054, 5,294,722 and 4,960,786 and European patent applications EP 429 257, EP 483 881, EP 547 556, EP 639 573 and EP 1 314 733. In particular European patent application EP 488 532 and US patents Nos. 5,236,916 and 5,374,615 disclose 1(N)-phenylindole-2-carboxylates as antihypertensive agents

and as chemical intermediates. However, none of these documents disclose or suggest the use of such compounds in the treatment of inflammation.

Indoles have also been disclosed for potential use in the treatment of inflammation in international patent applications WO 99/43672, WO 98/08818, WO 99/43654, WO 99/43651, WO 99/05104 and WO 03/029212, European patent application EP 986 666 and US patents Nos. 6,500,853 and 6,630,496. 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.

International patent application WO 01/30343, and European patent application EP 186 367, also mention indoles for potential use as PPAR- γ binding agents, and in the treatment of inflammation, respectively. However, these documents do not mention or suggest compounds in which the benzenoid moiety of the indole is either substituted with an aromatic ring or directly substituted with a cycloalkyl or heterocycloalkyl ring. Further, Dropinski *et al*, *Bioorganic and Medicinal Chemistry Letters*, 15 (2005) 5035-5038 discloses various indoles for use as PPAR- γ partial agonists. There is no mention or suggestion of the use of such compounds as inhibitors of mPGES in that document.

Various 1(N)-benzylindole-2-carboxylates and derivatives thereof are known from international patent applications WO 99/33800 as Factor Xa inhibitors; WO 99/07678, WO 99/07351, WO 00/46198, WO 00/46197, WO 00/46195 and WO 00/46199 as inhibitors of MCP-1; international patent application WO 96/18393 as inhibitors of IL-8; international patent applications WO 93/25546 and WO 94/13662, European patent application EP 535 924 A1 and US patent No. 5,081,138 as inhibitors of leukotriene biosynthesis; international patent application WO 02/30895 as PPAR- γ binding agents; and European patent application EP 166 591 as prostaglandin antagonists. Further, international patent application WO 2005/005415 discloses such compounds for use as inhibitors of mPGES and thus in the treatment of inflammation. 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.

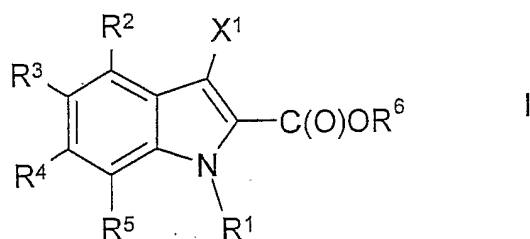
Further, unpublished international patent applications PCT/GB2005/002404,
5 PCT/GB2005/002391 and PCT/GB2005/002396 disclose indoles for use as inhibitors of mPGES and thus in the treatment of inflammation. However, there is no suggestion of indoles which are substituted at the benzenoid moiety of the indole with either a cycloalkyl or heterocycloalkyl group or with a aromatic group that is attached *via* a linking group.

10

Finally, international patent application WO 94/14434 discloses structurally similar indoles as endothelin receptor antagonists. There is no specific disclosure in this document of indole-2-carboxylates in which an aromatic group is directly attached *via* the indole nitrogen, nor of compounds in which aromatic and
15 heteroaromatic moieties are attached, *via* a linking group, or cycloalkyl and heterocycloalkyl moieties are attached, to the benzenoid part of the indole.

Disclosure of the Invention

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



wherein

25

one of the groups R², R³, R⁴ and R⁵ represents -D-E, a cycloalkyl group or a heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from G¹ and/or Z¹) and:

- a) the other groups are independently selected from hydrogen, G^1 , 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, in the case when one of R^2 , R^3 , R^4 and R^5 represents -D-E, an aryl group and a heteroaryl group (which latter two groups are optionally substituted by one or more substituents selected from A); 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, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^6$, $-OR^6$ and $=O$;

D represents $-O-$, $-C(R^7)(R^8)-$, C_{2-4} alkylene, $-C(O)-$ or $-S(O)_m-$;

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

R^7 and R^8 independently represent H, halo or C_{1-6} alkyl, which latter group is optionally substituted by halo, or R^7 and R^8 may together form, along with the carbon atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains a heteroatom and is optionally substituted by one or more substituents selected from halo and C_{1-3} alkyl, which latter group is optionally substituted by one or more halo substituents;

- X^1 represents H, halo, $-N(R^9)-J-R^{10}$ or $-Q-X^2$;

J represents a single bond, $-C(O)-$ or $-S(O)_m-$;

- Q represents a single bond, $-O-$, $-C(O)-$ or $-S(O)_m-$;

m represents, on each occasion when mentioned above, 0, 1 or 2;

X^2 represents:

- (a) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from A; or
- 5 (b) 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 ;

R^6 , R^9 and R^{10} independently represent, on each occasion when mentioned above:

- I) hydrogen;
- 10 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 ; or
- R^9 and R^{10} may be linked together to form, along with the N atom and the J group
- 15 to which R^9 and R^{10} are respectively attached, a 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^1 and/or Z^1 ;

A represents, on each occasion when mentioned above:

- 20 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 ; or
- III) a G^1 group;

25

G^1 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^{11a}$;

wherein A^1 represents a single bond or a spacer group selected from $-C(O)A^2-$, $-S(O)_2A^3-$, $-N(R^{12a})A^4-$ or $-OA^5-$, in which:

- 30 A^2 represents a single bond, $-O-$, $-N(R^{12b})-$ or $-C(O)-$;
- A^3 represents a single bond, $-O-$ or $-N(R^{12c})-$;

A^4 and A^5 independently represent a single bond, $-C(O)-$, $-C(O)N(R^{12d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{12e})-$;

Z^1 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{11b}$,
 5 $=NS(O)_2N(R^{12f})R^{11c}$, $=NCN$ 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 ;
- 10 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 ; or
- III) a G^2 group;

G^2 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$,
 15 $-ONO_2$ or $-A^6-R^{13a}$;

wherein A^6 represents a single bond or a spacer group selected from $-C(O)A^7-$, $-S(O)_2A^8-$, $-N(R^{14a})A^9-$ or $-OA^{10}-$, in which:

A^7 represents a single bond, $-O-$, $-N(R^{14b})-$ or $-C(O)-$;

A^8 represents a single bond, $-O-$ or $-N(R^{14c})-$;

20 A^9 and A^{10} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{14d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{14e})-$;

Z^2 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{13b}$,
 25 $=NS(O)_2N(R^{14f})R^{13c}$, $=NCN$ or $=C(H)NO_2$;

R^{11a} , R^{11b} , R^{11c} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , R^{12e} , R^{12f} , R^{13a} , R^{13b} , R^{13c} , R^{14a} , R^{14b} , R^{14c} ,
 R^{14d} , R^{14e} and R^{14f} 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 ;
- 30 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^{11a} to R^{11c} and R^{12a} to R^{12f} , and/or R^{13a} to R^{13c} and R^{14a} to R^{14f} , 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
 5 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 $-A^{11}-R^{15a}$;

wherein A^{11} represents a single bond or a spacer group selected from $-C(O)A^{12}-$,
 10 $-S(O)_2A^{13}-$, $-N(R^{16a})A^{14}-$ or $-OA^{15}-$, in which:

A^{12} represents a single bond, $-O-$, $-N(R^{16b})-$ or $-C(O)-$;

A^{13} represents a single bond, $-O-$ or $-N(R^{16c})-$;

A^{14} and A^{15} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{16d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{16e})-$;

15

Z^3 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{15b}$, $=NS(O)_2N(R^{16f})R^{15c}$, $=NCN$ or $=C(H)NO_2$;

R^{15a} , R^{15b} , R^{15c} , R^{16a} , R^{16b} , R^{16c} , R^{16d} , R^{16e} and R^{16f} are independently selected
 20 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, $-N(R^{17a})R^{18a}$, $-OR^{17b}$ and $=O$; and

25 iii) an aryl or heteroaryl group, both of which are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{17c})R^{18b}$ and $-OR^{17d}$; or any pair of R^{15a} to R^{15c} and R^{16a} to R^{16f} 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
 30 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, $-N(R^{17e})R^{18c}$, $-OR^{17f}$ and $=O$;

R^{17a} , R^{17b} , R^{17c} , R^{17d} , R^{17e} , R^{17f} , R^{18a} , R^{18b} and R^{18c} are independently selected from hydrogen and C_{1-4} alkyl, which latter group is optionally substituted by one or more halo groups;

5

or a pharmaceutically-acceptable salt thereof,

provided that, when R^3 represents -D-E, in which D represents $-C(R^7)(R^8)-$, X^1 , R^2 , R^4 , R^5 , R^7 and R^8 all represent H and:

- 10 (a) E represents a 2-butyl-5-hydroxymethyl-1*H*-imidazol-1-yl group, then R^6 does not represent H when R^1 represents phenyl or 2-carboxyphenyl;
- (b) E represents a 2-butyl-5-hydroxymethyl-1*H*-imidazol-1-yl group or a 2-butyl-5-formyl-1*H*-imidazol-1-yl group, then R^6 does not represent ethyl when R^1 represents phenyl or 2-ethoxycarbonylphenyl;
- 15 (c) E represents a 2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl group, then R^6 does not represent H or ethyl when R^1 represents 2-(1*H*-tetrazol-5-yl)phenyl; or
- (d) E represents a 2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl group or a 2-butyl-4-chloro-5-formyl-1*H*-imidazol-1-yl group, then R^6 does not represent
- 20 ethyl when R^1 represents 2-cyanophenyl,

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

- 25 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
- 30 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* (5 *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 (10 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. (15 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 (20 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 (25 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, and C_{1-q} alkylene, groups (where q is the (30 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, in the case of alkyl, cyclic (so forming a C_{3-q}

cycloalkyl group). 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 and alkylene 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, in the case of alkyl, a C_{2-q} alkenyl or a C_{2-q} alkynyl group or, in the case of alkylene, a C_{2-q} alkenylene or a C_{2-q} alkynylene group).

Cycloalkyl groups that may be mentioned include non-aromatic C₃₋₁₆, such as C₃₋₁₀, cycloalkyl groups. C_{3-q} cycloalkyl groups (where q is the appropriate upper limit of the range) may be monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged (so forming, for example, fused ring systems such as three fused cycloalkyl groups). Such cycloalkyl groups may be saturated or unsaturated containing one or more double or triple bond (forming for example a C_{3-q} cycloalkenyl or a C_{8-q} cycloalkynyl group). Cycloalkyl groups that may be mentioned include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclooctynyl, bicycloheptyl, bicyclooctyl, and bicyclooctenyl, as well as bridged cycloalkyl groups, such as adamantyl, noradamantyl, norbornane, norbornene and norbornadiene groups. Substituents may be attached at any point on the cycloalkyl 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. Preferred cycloalkyl groups include optionally substituted C₃₋₈ cycloalkyl groups, which groups optionally contain one unsaturation (e.g. a double bond). Cycloalkyl groups that may be mentioned include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl (e.g. cyclopenten-1-yl), cyclohexenyl (e.g. cyclohexen-1-yl) and norbornanyl (e.g. norbornan-2-yl).

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

30

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic and bicyclic heterocycloalkyl groups (which groups may further be bridged) 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} 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 7-azabicyclo[2.2.1]heptanyl, 6-azabicyclo[3.1.1]heptanyl, 6-azabicyclo[3.2.1]octanyl, 8-azabicyclo[3.2.1]octanyl, aziridinyl, azetidiny, 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, imidazoliny, morpholiny, 7-oxabicyclo[2.2.1]heptanyl, 6-oxabicyclo[3.2.1]octanyl, oxetanyl, oxiranyl, piperazinyl, piperidinyl, pyranly, pyrazolidinyl, pyrrolidinonyl, pyrrolidinyl, pyrroliny, quinuclidinyl, sulfolanyl, 3-sulfolenyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydropyridyl (such as 1,2,3,4-tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietanyl, thiiranyl, thiolanyl, thiomorpholiny, trithianyl (including 1,3,5-trithianyl), tropanyl and the like. 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. When, for example, one of R², R³, R⁴ and R⁵ represents a cycloalkyl or a heterocycloalkyl group, preferred heterocycloalkyl groups include optionally substituted 5 to 6-membered heterocyclic groups containing at least one oxygen or, more preferably, nitrogen atom and, optionally, a further nitrogen and/or oxygen atom. Heterocycloalkyl groups that may be mentioned include optionally substituted pyrrolidinyl (e.g. pyrrolidin-1-yl),

morpholinyl (e.g. 4-morpholin-1-yl), piperazinyl (e.g. piperazin-1-yl), piperidinyl (e.g. piperidin-1-yl and piperidin-4-yl) and tetrahydropyridyl (e.g. 1,2,3,6-tetrahydropyridin-2-yl) groups.

- 5 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
10 either an alkylene or heteroalkylene chain (as appropriate).

Aryl groups that may be mentioned include C₆₋₁₄ (such as C₆₋₁₃ (e.g. C₆₋₁₀)) aryl groups. Such groups may be monocyclic, bicyclic or tricyclic and have between 6 and 14 ring carbon atoms, in which at least one ring is aromatic. C₆₋₁₄ aryl groups
15 include phenyl, naphthyl and the like, such as 1,2,3,4-tetrahydronaphthyl, indanyl, indenyl and fluorenyl. 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 linked to the rest of the molecule *via* an aromatic ring.

- 20 Heteroaryl groups that may be mentioned include those which have between 5 and 14 (e.g. 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 benzothiadiazolyl (including
25 2,1,3-benzothiadiazolyl), isothiochromanyl and, more preferably, acridinyl, benzimidazolyl, benzodioxanyl, benzodioxepinyl, benzodioxolyl (including 1,3-benzodioxolyl), benzofuranyl, benzofurazanyl, benzothiazolyl, benzoxadiazolyl (including 2,1,3-benzoxadiazolyl), benzoxazinyl (including 3,4-dihydro-2*H*-1,4-benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including
30 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl,

isothiazoliyl, isoxazoliyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazoliyl (including 1,2,3-oxadiazoliyl, 1,2,4-oxadiazoliyl and 1,3,4-oxadiazoliyl), oxazoliyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazoliyl, 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), tetrazoliyl, thiadiazoliyl (including 1,2,3-thiadiazoliyl, 1,2,4-thiadiazoliyl and 1,3,4-thiadiazoliyl), thiazoliyl, thiochromanyl, thienyl, triazoliyl (including 1,2,3-triazoliyl, 1,2,4-triazoliyl and 1,3,4-triazoliyl) 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. Heteroaryl groups may also be in the *N*- or *S*- oxidised form.

Heteroatoms that may be mentioned include phosphorus, silicon, boron, tellurium, selenium and, preferably, oxygen, nitrogen and sulphur.

20

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^2 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^2 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.

30

For the avoidance of doubt, when a term such as " R^2 to R^5 " is employed herein, this will be understood by the skilled person to mean R^2 , R^3 , R^4 and R^5 inclusively.

- 5 As stated hereinbefore, any pair of R^{11a} to R^{11c} and R^{12a} to R^{12f} , may be linked as hereinbefore defined. For the avoidance of doubt, such R^{11a} to R^{11c} groups, and R^{12a} to R^{12f} groups may be attached to a single nitrogen atom (e.g. R^{11a} and R^{12a} or R^{11c} and R^{12f}), which may form part of the ring.
- 10 Compounds of the invention that may be mentioned include those in which one of the groups R^2 , R^3 , R^4 and R^5 represents -D-E as hereinbefore defined.

Compounds of the invention that may be mentioned also include those in which one of the groups R^2 , R^3 , R^4 and R^5 represents a cycloalkyl group or a
15 heterocycloalkyl group, both of which are optionally substituted as hereinbefore defined.

Compounds of the invention that may be mentioned include those in which when one of the groups R^2 , R^3 , R^4 and R^5 represents -D-E then:

- 20 a) the other groups are independently selected from hydrogen, G^1 , 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
25 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 $=O$.

Further compounds of the invention that may be mentioned include those in
30 which, when one of the groups R^2 , R^3 , R^4 and R^5 represents optionally substituted cycloalkyl or heterocycloalkyl as hereinbefore defined or, more particularly, -D-E and one or more of the other groups represent G^1 then, when G^1 represents

$-A^1-R^{11a}$, A^1 represents a single bond, then R^{11a} represents hydrogen, C_{1-8} alkyl or a heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from G^3 and/or Z^3).

- 5 Yet further compounds of the invention that may be mentioned include those in which, when one of the groups R^2 , R^3 , R^4 and R^5 represents optionally substituted cycloalkyl or heterocycloalkyl as hereinbefore defined or, more particularly, -D-E and one or more of the other groups represent G^1 then, when G^1 represents $-A^1-R^{11a}$, A^1 represents a spacer group selected from $-C(O)A^2-$, $-S(O)_2A^3-$,
 10 $-N(R^{12a})A^4-$ or $-OA^5-$.

Compounds of the invention that may be mentioned also include those in which, for example, when one of the groups R^2 , R^3 , R^4 and R^5 represents optionally substituted cycloalkyl or heterocycloalkyl as hereinbefore defined or, more particularly, -D-E, and X^1 represents $-Q-X^2$, Q is a single bond and X^2 is either:

- (a) an aryl group or a heteroaryl group, which groups are substituted by A in which A is G^1 ; or
 (b) C_{1-8} alkyl or a heterocycloalkyl group, which groups are substituted by G^1 , and, in either case, G^1 is $-A^1-R^{11a}$, then A^1 represents a single bond or a spacer
 20 group selected from $-C(O)-$, $-S(O)_2-$, $-S(O)_2N(R^{12c})-$, $-N(R^{12a})A^4-$ or $-OA^5-$.

Further compounds of the invention that may be mentioned include those in which, when one of the groups R^2 , R^3 , R^4 and R^5 represents optionally substituted cycloalkyl or heterocycloalkyl as hereinbefore defined or, more particularly, -D-E, and X^1 represents $-Q-X^2$, Q is a single bond, X^2 is C_{1-8} alkyl substituted by G^1 , G^1 is $-A^1-R^{11a}$, A^1 is a single bond, R^{11a} represents an aryl group, a heteroaryl group or a heterocycloalkyl group, all of which groups are substituted by G^3 , and G^3 is $-A^{11}-R^{15a}$, then A^{11} represents a single bond or a spacer group selected from $-C(O)-$, $-S(O)_2-$, $-S(O)_2N(R^{16c})-$, $-N(R^{16a})A^{14}-$ or $-OA^{15}-$.

30

Yet further compounds of the invention that may be mentioned include those in which when one of the groups R^2 , R^3 , R^4 and R^5 represents optionally substituted

cycloalkyl or heterocycloalkyl as hereinbefore defined or, more particularly, -D-E and X² represents C₁₋₈ alkyl terminally substituted by both Z¹ and G¹, in which Z¹ represents =O and G¹ represents -A¹-R^{11a}, then when A¹ represents -N(R^{12a})A⁴-, A⁴ represents -C(O)-, -C(O)N(R^{12d})-, -C(O)O- or -S(O)₂N(R^{12e}), and when A¹ represents -OA⁵-, A⁵ represents -C(O)-, -C(O)N(R^{12d})-, -C(O)O-, -S(O)₂- or -S(O)₂N(R^{12e}).

Further compounds of the invention that may be mentioned include those in which, when R³ represents -D-E, in which D represents -C(R⁷)(R⁸)- and R⁷ and R⁸ both represent H, then E does not represent an optionally substituted imidazolyl (e.g. imidazol-1-yl) group, and particularly an optionally substituted 2-butyl-1*H*-imidazol-1-yl (such as a 2-butyl-5-hydroxymethyl-1*H*-imidazol-1-yl, 2-butyl-5-formyl-1*H*-imidazol-1-yl, 2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl, or a 2-butyl-4-chloro-5-formyl-1*H*-imidazol-1-yl, group).

15

Still further compounds of the invention that may be mentioned include those in which:

- (i) when R³ represents -D-E, in which D represents -C(R⁷)(R⁸)-, R⁷ and R⁸ do not both represent H when E represents a heteroaryl group;
- (ii) when R³ represents -D-E, in which D represents -C(R⁷)(R⁸)-, R⁷ and R⁸ do not both represent H;
- (iii) when D represents -C(R⁷)(R⁸)-, R⁷ and R⁸ do not both represent H.

Yet further compounds of the invention that may be mentioned include those in which D represents C₂₋₄ alkylene or, more preferably, -O-, -C(O)- or -S(O)_m-.

25

Preferred compounds of the invention include those in which:

when one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, then it is preferably R³ or R⁴;

Q represents -O-, -S- or, more preferably, a single bond;

30

A represents C₁₋₆ alkyl optionally substituted by one or more G¹ groups or (more preferably, in the case where one of R² to R⁵ represents a cycloalkyl or heterocycloalkyl group) G¹;

5 X² represents C₁₋₆ (e.g. C₁₋₄) alkyl or heterocycloalkyl, both of which are optionally substituted (and preferably substituted in the case where one of R² to R⁵ represents a cycloalkyl or heterocycloalkyl group) by one or more (e.g. one) G¹ and/or Z¹ groups;

R⁹ represents H or C₁₋₂ alkyl (e.g. methyl);

10 R¹⁰ represents heteroaryl or, preferably, C₁₋₆ (such as C₁₋₄ (e.g. C₁₋₃)) alkyl, which group may be unsubstituted or is (e.g. preferably) substituted by one or more (e.g. one) groups selected from G¹;

R⁹ and R¹⁰ are linked to form a 4- to 7-membered (e.g. 5- or 6-membered) ring, which ring may, for example preferably, contain (in addition to the nitrogen atom to which R⁹ is attached) a further heteroatom (e.g. nitrogen or oxygen) and which
15 ring is optionally substituted by one or more (e.g. two) Z¹ groups;

G¹ represents halo, cyano, -NO₂ or -A¹-R^{11a};

when one of R² to R⁵ represents -D-E-, then A¹ represents a single bond, -C(O)A²-, -N(R^{12a})A⁴- or, preferably, -OA⁵-;

20 when one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, then A¹ represents -N(R^{12a})A⁴- or, more preferably, a single bond, -C(O)A²- or -OA⁵-;

A² represents -O- or, in the case where one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, -N(R^{12b})-;

A⁴ and A⁵ independently represent -C(O)-, -C(O)N(R^{12d})-, -C(O)O- or, preferably
25 in the case where any one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, a single bond;

Z¹ represents =NOR^{11b}, =NCN or, preferably, =O;

when one of R² to R⁵ represents -D-E-, then R^{11a}, R^{11b} and R^{11c} independently represent hydrogen, an aryl group, a heteroaryl group, a heterocycloalkyl group
30 (such as C₄₋₈ heterocycloalkyl, which group contains one oxygen or, more preferably, nitrogen atom and, optionally, a further nitrogen or oxygen atom) or, preferably, C₁₋₆ (e.g. C₁₋₄) alkyl, which latter four groups are optionally substituted

by one or more G^3 groups and/or (in the case of alkyl and heterocycloalkyl) Z^3 groups;

when one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group, then R^{11a} , R^{11b} and R^{11c} independently represent aryl or, preferably, H or, more preferably, C_{1-7} alkyl, C_{4-8} heterocycloalkyl (which heterocycloalkyl group contains one oxygen or, more preferably, nitrogen atom and, optionally, a further nitrogen or oxygen atom) or a heteroaryl group, which latter three groups are optionally substituted by one or more G^3 groups and/or (in the case of alkyl and heterocycloalkyl) Z^3 groups;

10 R^{12a} , R^{12b} , R^{12c} , R^{12d} , R^{12e} and R^{12f} independently represent H or (more preferably, in the case where one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group) C_{1-2} alkyl;

G^2 represents cyano, $-N_3$ or, more preferably, halo, $-NO_2$ or $-A^6-R^{13a}$;

A^6 represents $-N(R^{14a})A^9-$ or $-OA^{10}-$;

15 A^9 represents $-C(O)N(R^{14d})-$, $-C(O)O-$ or, more preferably, a single bond or $-C(O)-$;

A^{10} represents a single bond;

Z^2 represents $=NOR^{13b}$ or $=NCN$ or, more preferably, $=O$;

G^3 represents halo, $-NO_2$ or $-A^{11}-R^{15a}$;

20 A^{11} represents $-N(R^{16a})-$ or $-O-$;

Z^3 represents $=O$;

J represents a single bond or, preferably, $-C(O)-$ or $-S(O)_2-$;

when any one of R^{15a} , R^{15b} , R^{15c} , R^{16a} , R^{16b} , R^{16c} , R^{16d} , R^{16e} and R^{16f} represents optionally substituted C_{1-6} alkyl, the optional substituent is one or more halo

25 groups;

when any one of R^{17a} , R^{17b} , R^{17c} , R^{17d} , R^{17e} , R^{17f} , R^{18a} , R^{18b} and R^{18c} represents optionally substituted C_{1-4} alkyl, the optional substituent is one or more fluoro groups.

30 Preferred aryl and heteroaryl groups that R^1 , E and (when they represent such aryl or heteroaryl groups) X^2 , R^9 and R^{10} may represent include 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, quinoliziny, benzofuranyl, isobenzofuranyl, chromanyl, 5 benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, benzimidazolyl, quinazolinyl, quinoxaliny, 1,3-benzodioxolyl, tetrazolyl, benzothiazolyl, and/or benzodioxanyl, groups.

Preferred values of R¹ include optionally substituted phenyl, pyridyl (e.g. 2- 10 pyridyl or 3-pyridyl) and imidazolyl.

Preferred values of E include optionally substituted 1,3-benzodioxolyl (e.g. 1,3-benzodioxol-5-yl), preferably, pyridyl (e.g. 2- or 3-pyridyl), imidazolyl, more preferably quinolinyl (e.g. 3-quinolinyl), and particularly phenyl.

15

Optional substituents on R¹, R², R³, R⁴, R⁵, X² and E groups are preferably selected from:

aryl (e.g. phenyl);

in the case of substituents on non-aromatic groups (e.g. cycloalkyl or 20 heterocycloalkyl groups), =O; or, more preferably,

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

cyano;

-NO₂;

C₁₋₆ alkyl, which alkyl group may be linear or branched (e.g. C₁₋₄ alkyl (including 25 ethyl, *n*-propyl, isopropyl, *n*-butyl or, preferably, methyl 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 30 (so forming, for example, fluoromethyl, difluoromethyl or, preferably, trifluoromethyl);

heterocycloalkyl, such as a C₄₋₅ heterocycloalkyl group, preferably containing a nitrogen atom and, optionally, a further nitrogen or oxygen atom, so forming for example morpholinyl (e.g. 4-morpholinyl), piperazinyl (e.g. 4-piperazinyl) or piperidinyl (e.g. 1-piperidinyl and 4-piperidinyl) or pyrrolidinyl (e.g. 1-pyrrolidinyl), which heterocycloalkyl group is optionally substituted by one or more (e.g. one or two) substituents selected from C₁₋₃ alkyl (e.g. methyl) and =O; -OR¹⁹; -N(R¹⁹)R²⁰; and in the case where one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, -C(O)OR¹⁹; wherein R¹⁹ and R²⁰ independently represent, on each occasion when mentioned above, H or C₁₋₆ alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl and, preferably, in the case where one of R² to R⁵ represents -D-E, methyl or isopropyl and, in the case where one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, isopropyl or *t*-butyl (which alkyl groups are optionally substituted by one or more halo (e.g. fluoro) groups (to form e.g. a trifluoromethyl group)).

Preferred values of R⁶ include C₁₋₄ alkyl and, particularly, H.

More preferred compounds of the invention include those in which, when one of R² to R⁵ represents -D-E-, then:

one of R⁴ and, more preferably, R³ represents -D-E and the other (more preferably) represents H;

D represents -CH₂-, preferably ethylene (e.g. ethynylene), -S-, -S(O)-, -S(O)₂- or, more preferably, -O- or -C(O)-;

X¹ represents -N(R⁹)-J-R¹⁰ or, more preferably, C₁₋₃ alkyl (e.g. methyl), heterocycloalkyl (which latter two groups are optionally substituted by G¹ and, preferably, -N(R^{12a})R^{11a}, -OR^{11a}, -R^{11a} or halo (e.g. fluoro or chloro)), H or halo (e.g. fluoro or chloro);

R² represents chloro or, preferably H;

R⁵ represents H;

- A represents G^1 , or C_{1-6} (e.g. C_{1-4}) alkyl (e.g. cyclohexyl or, preferably, methyl or *t*-butyl) optionally substituted by one or more G^1 groups;
 G^1 represents cyano or, preferably, fluoro, chloro, $-NO_2$ or $-A^1-R^{11a}$;
 A^4 represents $-C(O)-$ or, preferably, a single bond;
 5 A^5 represents a single bond;
 R^9 represents H or methyl,
 R^{10} represents methyl, *t*-butyl, pyridyl (e.g. 3-pyridyl), propyl (e.g. *n*-propyl optionally substituted by a G^1 (e.g. $-N(R^{12a})R^{11a}$) group); or
 R^9 and R^{10} are linked to form a 5- or 6-membered (e.g. 5-membered) ring, which
 10 is substituted by one Z^1 group;
 R^{11a} , R^{11b} and R^{11c} independently represent a phenyl group, a heteroaryl (such as tetrazolyl (e.g. 5-tetrazolyl), imidazolyl (e.g. 4-imidazolyl or 2-imidazolyl) or a pyridyl (e.g. 3-pyridyl, 4-pyridyl or, especially, 2-pyridyl)) group, or, more preferably, C_{1-3} alkyl (e.g. methyl or isopropyl) optionally substituted by one or
 15 more G^3 groups;
 R^{12a} , R^{12b} , R^{12c} , R^{12d} , R^{12e} and R^{12f} independently represent H or methyl;
 G^3 represents halo (e.g. fluoro).

- Further preferred compounds of the invention include those in which, when one of
 20 R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group as hereinbefore defined, then:
 one of R^3 and R^4 represents an optionally substituted cycloalkyl group, or an optionally substituted heterocycloalkyl group, as specified hereinbefore, and the other represents H;
 25 X^1 represents $-N(R^9)-J-R^{10}$, preferably, H, C_{1-3} alkyl, heterocycloalkyl (which latter two groups are preferably substituted by $-N(R^{12a})R^{11a}$, $-OR^{11a}$ or $-R^{11a}$) or, more preferably, halo (e.g. fluoro or, particularly, chloro);
 R^2 and/or R^5 independently represent H;
 A represents G^1 ;
 30 G^1 represents fluoro, chloro or $-A^1-R^{11a}$;
 A^2 represents $-O-$;
 A^5 represents a single bond;

R^{11a} , R^{11b} and R^{11c} independently represent an aryl (e.g. phenyl) group or, preferably, a heteroaryl group (such as tetrazolyl (e.g. 5-tetrazolyl) or, more preferably, pyridyl (e.g. 2-pyridyl, 3-pyridyl or 4-pyridyl) or imidazolyl (e.g. 4-imidazolyl or 2-imidazolyl)), more preferably, C_{1-6} alkyl (e.g. methyl, isopropyl, *t*-butyl or cyclopentyl) or C_{4-6} heterocycloalkyl (e.g. pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl), all of which are optionally substituted by one or more G^3 groups;

R^{12a} , R^{12b} , R^{12c} , R^{12d} , R^{12e} and R^{12f} independently represent H or methyl;

G^3 represents halo (e.g. fluoro).

10

Most preferred compounds of the invention that may be mentioned include those in which X^1 groups (e.g. when one of R^2 to R^5 represents -D-E) represent H, chloro, $-C_2H_5CN$, pyrrolidinyl (e.g. 2-oxopyrrolidin-1-yl), $-N(CH_3)C(O)CH_3$, $-N(H)C(O)t$ -butyl, $-N(H)C(O)CH_3$, $-N(H)C(O)$ -pyrid-3-yl, $-N(H)S(O)_2CH_3$, $-N(H)C(O)C_3H_6N(CH_3)_2$, $-N(H)C_3H_6-N(CH_3)_2$ or $-N(H)C(O)t$ -butyl.

15

Values of R^1 that may be mentioned include 4-methyl-3-nitrophenyl, 4-acetamidophenyl or, preferably, 4-cyclopropyloxyphenyl, 4-cyclopentyloxyphenyl and 4-isopropoxyphenyl.

20

Values of E that may be mentioned include unsubstituted phenyl, isopropoxyphenyl (e.g. 2-, 3 or 4-isopropoxyphenyl), trifluoromethoxyphenyl (e.g. 3- or 4-trifluoromethoxyphenyl), dichlorophenyl (e.g. 3,5- or 3,4-dichlorophenyl), 4-*tert*-butylphenyl, chlorophenyl (e.g. 4-chlorophenyl), trifluoromethylphenyl (e.g. 3-trifluoromethylphenyl), trifluoromethoxyphenyl (e.g. 3- or 4-trifluoromethoxyphenyl), chloropyridyl (e.g. 6-chloropyrid-3-yl or 6-chloropyrid-2-yl), benzodioxolyl (e.g. 1,3-benzodioxol-5-yl or 2,2-difluoro-1,3-benzodioxol-5-yl), 3-trifluoromethoxy-4-chlorophenyl, 3-trifluoromethoxy-4-isopropoxyphenyl, 3-fluoro-4-trifluoromethoxyphenyl or, preferably, 3-chlorophenyl, 4-trifluoromethylphenyl, 5-trifluoromethoxypyridin-2-yl, 6-trifluoromethoxypyridin-3-yl and 4-cyclohexylphenyl.

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30

Particularly preferred values of cycloalkyl or heterocycloalkyl groups that R^2 to R^5 may represent include 1-piperidinyl, 2-phenylcyclopropyl, 5-*tert*-butyl-2-hydroxycyclohexyl and 5-*tert*-butyl-2-oxo-cyclohexyl.

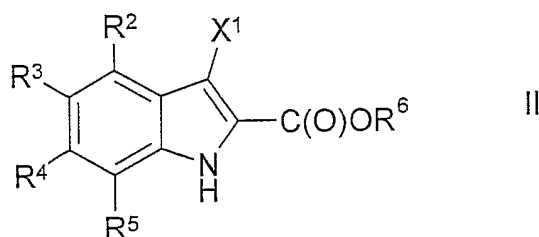
- 5 Particularly preferred values of X^2 include C_{1-3} alkyl (e.g. methyl), which group is unsubstituted or, preferably, substituted by one or more halo (e.g. fluoro or chloro) groups so forming, for example, a trifluoromethyl group.

10 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.

- 15 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,



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

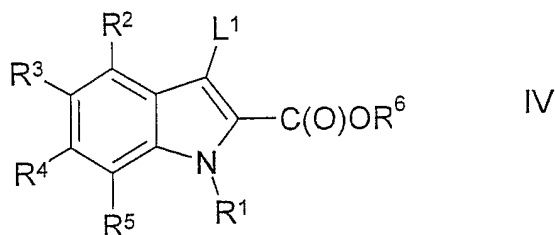
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wherein L^1 represents a suitable leaving group such as chloro, bromo, iodo, a sulfonate group (e.g. $-\text{OS}(\text{O})_2\text{CF}_3$, $-\text{OS}(\text{O})_2\text{CH}_3$, $-\text{OS}(\text{O})_2\text{PhMe}$ or a nonaflate) or $-\text{B}(\text{OH})_2$ 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, Pd₂(dba)₃ or NiCl₂ and an optional additive such as Ph₃P, 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, Et₃N, pyridine, *N,N*-dimethylethylenediamine, Na₂CO₃, K₂CO₃, K₃PO₄, Cs₂CO₃, *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 R¹ represents phenyl and L¹ 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) for compounds of formula I in which X¹ represents -Q-X², in which Q is a single bond or -C(O)-, reaction of a compound of formula IV,



wherein L¹, R¹, R², R³, R⁴, R⁵ and R⁶ are as hereinbefore defined, with a compound of formula V,



wherein Q^a represents a single bond or -C(O)-, L² 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), $-\text{Sn}(\text{alkyl})_3$ (e.g. $-\text{SnMe}_3$ or $-\text{SnBu}_3$), or a similar group known to the skilled person, and X^2 is as hereinbefore defined. The skilled person will appreciate that L^1 and L^2 will be mutually compatible. In this respect, preferred leaving groups for compounds of formula V in which Q^a is

5 $-\text{C}(\text{O})-$ include chloro or bromo groups, and preferred leaving groups for compounds of formula V in which Q^a is a single bond include $-\text{B}(\text{OH})_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl, 9-borabicyclo[3.3.1]nonane (9-BBN), or $-\text{Sn}(\text{alkyl})_3$. 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,

10 Pd/C, PdCl_2 , $\text{Pd}(\text{OAc})_2$, $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$, $\text{Pd}(\text{Ph}_3\text{P})_4$, $\text{Pd}_2(\text{dba})_3$ or NiCl_2 and a ligand such as *t*-Bu₃P, (C₆H₁₁)₃P, Ph₃P, AsPh₃, P(*o*-Tol)₃, 1,2-bis(diphenylphosphino)ethane, 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl, 2,2'-bis(diphenylphosphino)-1,1'-bi-naphthyl, 1,1'-bis(diphenyl-phosphinoferrocene), 1,3-bis(diphenylphosphino)propane, xantphos, or a mixture thereof, together with a

15 ^a suitable base such as, Na₂CO₃, K₃PO₄, Cs₂CO₃, NaOH, KOH, K₂CO₃, CsF, Et₃N, (*i*-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

20 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 certain compounds of formula IV (in particular those in which L^1 represents chloro, bromo or iodo) are also compounds of formula I and therefore compounds of the invention. In the case where Q^a

25 represents a single bond and X^2 represents either C₂₋₈ alkenyl, cycloalkenyl or heterocycloalkenyl in which the double bond is between the carbon atoms that are α and β to L^2 , the skilled person will appreciate that the double bond may migrate on formation of the compound of formula I to form a double bond that is between the carbon atoms that are β and γ to the indole ring;

(iii) for compounds of formula I in which X^1 represents $-\text{Q}-\text{X}^2$ and Q represents $-\text{C}(\text{O})-$, reaction of a compound of formula I in which X^1 represents H with a

compound of formula V in which Q^a represents $-C(O)-$ and L^2 represents a suitable leaving group such as chloro or bromo, $-N(C_{1-6} \text{ alkyl})_2$ (e.g. $-N(CH_3)_2$) or a carboxylate group such as $-O-C(O)-X^{2y}$ in which X^{2y} represents X^2 or H. In the latter case, X^{2y} and X^2 are preferably the same, or X^{2y} represents e.g. H, CH_3 or CF_3 . This reaction may be performed under suitable conditions known to those skilled in the art, for example in the presence of a suitable Lewis acid (e.g. $AlCl_3$ or $FeCl_3$). Reaction of a compound of formula V in which L^2 represents $-N(C_{1-6} \text{ alkyl})_2$ and X^2 represents optionally substituted aryl (e.g. phenyl) or heteroaryl may be performed in the presence of a reagent such as $POCl_3$, for example under reaction conditions described in *Bioorg. Med. Chem. Lett.*, **14**, 4741-4745 (2004). The skilled person will appreciate that in the latter instance, $POCl_3$ may convert the compound of formula V into one in which L^2 represents chloro and/or Q^a represents a derivative of $-C(O)-$ (e.g. an iminium derivative), which group may be transformed back to a $-C(O)-$ group before or after reaction with the compound of formula I in which X^1 represents H;

(iv) for compounds of formula I in which X^1 represents $-N(R^9)-J-R^{10}$ or $-Q-X^2$ in which Q represents $-O-$ or $-S-$, reaction of a compound of formula IV as hereinbefore defined with a compound of formula VI,

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VI

in which X^{1b} represents $-N(R^9)-J-R^{10}$ or $-Q-X^2$ in which Q represents $-O-$ or $-S-$ and R^9 , J, R^{10} and X^2 are as hereinbefore defined, for example under reaction conditions such as those hereinbefore described in respect of either process (i) or (ii) above;

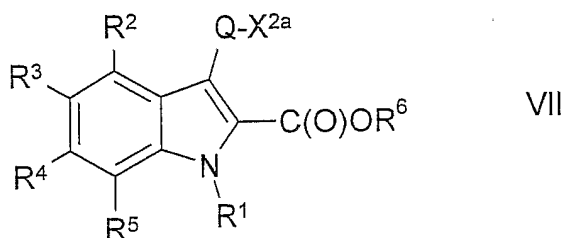
(v) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-S-$, reaction of a compound of formula I in which X^1 represents H, with a compound of formula VI in which X^{1b} represents $-Q-X^2$, Q represents $-S-$ and X^2 is as hereinbefore defined, for example in the presence of *N*-chlorosuccinimide and a suitable solvent (e.g. dichloromethane), e.g. as described in *inter alia Org.*

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Lett., 819-821 (2004). Alternatively, reaction of a compound of formula VI in which X^{1b} represents $-Q-X^2$, Q represents $-S-$ and X^2 represents an optionally substituted aryl (phenyl) or heteroaryl (e.g. 2-pyridyl) group, may be performed in the presence of PIFA ($\text{PhI}(\text{OC}(\text{O})\text{CF}_3)_2$) in a suitable solvent such as $(\text{CF}_3)_2\text{CHOH}$. Introduction of such an $-S-X^2$ group is described in *inter alia* *Bioorg. Med. Chem. Lett.*, **14**, 4741-4745 (2004);

(vi) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-S(\text{O})-$ or $-S(\text{O})_2-$, oxidation of a corresponding compound of formula I in which Q represents $-S-$ under appropriate oxidation conditions, which will be known to those skilled in the art;

(vii) for compounds of formula I in which X^1 represents $-Q-X^2$, X^2 represents C_{1-8} alkyl substituted by G^1 , G^1 represents $-A^1-R^{11a}$, A^1 represents $-N(R^{12a})A^4-$ and A^4 is a single bond (provided that Q represents a single bond when X^2 represents substituted C_1 alkyl), reaction of a compound of formula VII,



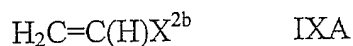
wherein X^{2a} represents a C_{1-8} alkyl group substituted by a $-Z^1$ group in which Z^1 represents $=\text{O}$, Q is as hereinbefore defined, provided that it represents a single bond when X^{2a} represents C_1 alkyl substituted by $=\text{O}$ (i.e. $-\text{CHO}$), and R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as hereinbefore defined under reductive amination conditions in the presence of a compound of formula VIII,



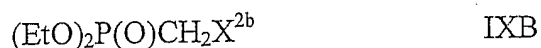
wherein R^{11a} and R^{12a} are as hereinbefore defined, under conditions well known to those skilled in the art;

(viiia) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond, X^2 represents methyl substituted by G^1 , G^1 represents $-A^1-R^{11a}$, A^1 represents $-N(R^{12a})A^4$, A^4 is a single bond and R^{11a} and R^{12a} are preferably methyl, reaction of a corresponding compound of formula I in which X^1 represents H, with a mixture of formaldehyde (or equivalent reagent) and a compound of formula VIII as hereinbefore defined (e.g. in which R^{11a} and R^{12a} represent methyl), for example in the presence of solvent such as a mixture of acetic acid and water, under e.g. standard Mannich reaction conditions known to those skilled in the art;

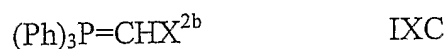
(viii) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents optionally substituted C_{2-8} alkenyl (in which a point of unsaturation is between the carbon atoms that are α and β to the indole ring), reaction of a corresponding compound of formula IV in which L^1 represents halo (e.g. iodo) with a compound of formula IXA,



or, depending upon the geometry of the double bond, reaction of a compound of formula VII in which Q represents a single bond and X^{2a} represents $-CHO$ with either a compound of formula IXB,



or the like, or a compound of formula IXC,

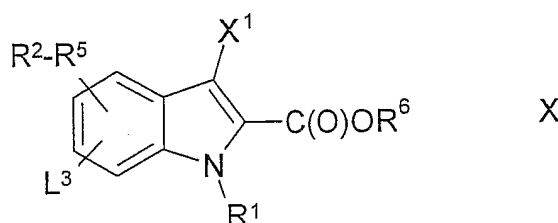


or the like, wherein, in each case, X^{2b} represents H, G^1 or C_{1-6} alkyl optionally substituted with one or more substituents selected from G^1 and/or Z^1 and G^1 and Z^1 are as hereinbefore defined, for example, in the case of a reaction of a

compound of formula IV with compound of formula IXA, in the presence of an appropriate catalyst (such as $\text{PdCl}_2(\text{PPh}_3)_2$), a suitable base (e.g. NaOAc and/or triethylamine) and an organic solvent (e.g. DMF) and, in the case of reaction of a compound of formula VII with either a compound of formula IXB, or IXC, under
 5 standard Horner-Wadsworth-Emmons, or Wittig, reaction conditions, respectively;

(ix) for compounds of formula I in which X^1 represents $-\text{Q}-\text{X}^2$ and X^2 represents optionally substituted, saturated C_{2-8} alkyl, saturated cycloalkyl, saturated
 10 heterocycloalkyl, C_{2-8} alkenyl, cycloalkenyl or heterocycloalkenyl, reduction (e.g. hydrogenation) of a corresponding compound of formula I in which X^2 represents optionally substituted C_{2-8} alkenyl, cycloalkenyl, heterocycloalkenyl, C_{2-8} alkynyl, cycloalkynyl or heterocycloalkynyl (as appropriate) under conditions that are known to those skilled in the art. For example, in the case where an alkynyl group
 15 is converted to a alkenyl group, in the presence of an appropriate poisoned catalyst (e.g. Lindlar's catalyst);

(x) for compounds of formula I in which one or more of R^2 , R^3 , R^4 and/or R^5 represents $-\text{D}-\text{E}$, in which D represents $-\text{C}(\text{O})-$, $-\text{C}(\text{R}^7)(\text{R}^8)-$, C_{2-4} alkylene or
 20 $-\text{S}(\text{O})_2-$, or optionally substituted cycloalkyl or heterocycloalkyl, reaction of a compound of formula X,



25 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, R^2-R^5 represents whichever of the three other substituents on the benzenoid ring, i.e. R^2 , R^3 , R^4 and R^5 , are already present in that ring, and X^1 , R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as hereinbefore defined, with, in the case where one of R^2 to R^5 represents

-D-E in which D represents -C(O)-, -C(R⁷)(R⁸)-, C₂₋₄ alkylene or -S(O)₂-, a compound of formula XI,



5

wherein D^a represents -C(O)-, -C(R⁷)(R⁸)- or C₂₋₄ alkylene or -S(O)₂-, L⁴ represents L¹ (when L³ is L²) or L² (when L³ is L¹), and L¹, L², E, R⁷ and R⁸ are as hereinbefore defined, or, in the case where one of R² to R⁵ represents an optionally substituted cycloalkyl or heterocycloalkyl group, a compound of formula XIA,

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wherein (R²⁻⁵) represents whichever one of the substituents R², R³, R⁴ or R⁵ is being introduced and L⁴, R², R³, R⁴ and R⁵ are as hereinbefore defined. For example, in the case of reaction with the compound of formula XIA or with the compound of formula XI in which D^a represents -C(O)- or C₂₋₄ alkylene, the reaction may be performed for example under similar conditions to those described hereinbefore in respect of process step (ii) above. Further, in the case of reaction with a compound of formula XI in which D^a represents -C(O)-, -C(R⁷)(R⁸)-, C₂₋₄ alkylene or -S(O)₂-, the reaction may be performed by first activating the compound of formula X. The skilled person will appreciate that compounds of formula X may first be activated when L³ represents halo, 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 C₁₋₆ alkyl-Mg-halide and ZnCl₂ or LiCl), followed by reaction with a compound of formula XI or XIA (as appropriate), optionally in the presence of a catalyst (e.g. FeCl₃) 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

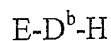
polar aprotic solvent such as THF)), followed by reaction with a compound of formula XI or XIA (as appropriate).

The skilled person will also appreciate that the magnesium of the Grignard reagent or the lithium of the lithiated species may be exchanged to 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 XI or XIA (as appropriate) under conditions known to those skilled in the art, for example such as those described hereinbefore in respect of process (ii) above;

10

(xi) for compounds of formula I in which when one of R^2 to R^5 represents -D-E- and D represents -S-, -O- or C_{2-4} alkynylene in which the triple bond is adjacent to E, reaction of a compound of formula X as hereinbefore defined in which L^3 represents L^2 as hereinbefore defined (for example $-\text{B}(\text{OH})_2$) with a compound of formula XII,

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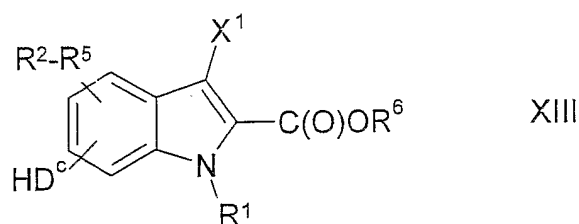
wherein D^b represents -S-, -O- or C_{2-4} alkynylene in which the triple bond is adjacent to E and E is as hereinbefore defined. Such reactions may be performed under similar conditions to those described hereinbefore in respect of process step (ii) above, for example in the presence of a suitable catalyst system, such as $\text{Cu}(\text{OAc})_2$, a suitable base, such as triethylamine or pyridine, and an appropriate organic solvent, such as DMF or dichloromethane;

25

(xii) for compounds of formula I in which when one of R^2 to R^5 represents -D-E- and D represents $-\text{S}(\text{O})-$ or $-\text{S}(\text{O})_2-$, oxidation of a corresponding compound of formula I in which D represents -S- under appropriate oxidation conditions, which will be known to those skilled in the art;

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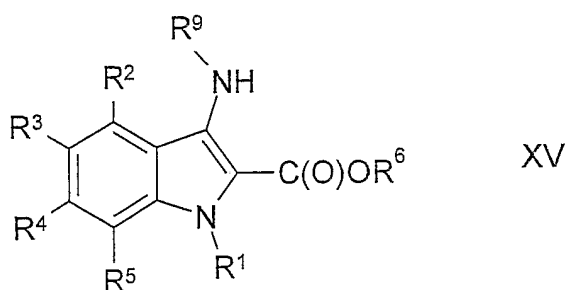
(xiii) for compounds of formula I in which when one of R^2 to R^5 represents -D-E- and D represents -O- or -S-, reaction of a compound of formula XIII,



- wherein the $-D^c-H$ group is attached to one or more of the carbon atoms of the
 5 benzenoid ring of the indole, D^c represents $-O-$ or $-S-$ and X^1 , R^1 , R^2-R^5 and R^6 are
 as hereinbefore defined, with a compound of formula XIV,



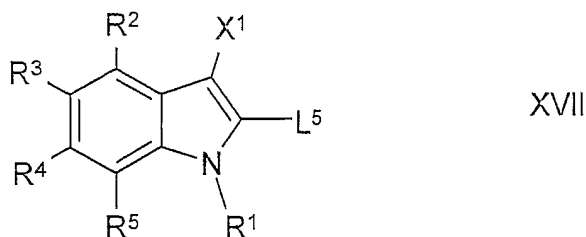
- 10 wherein L^2 is as hereinbefore defined (for example $-B(OH)_2$, chloro, bromo or
 iodo) and E is as hereinbefore defined, under conditions known to those skilled in
 the art, for example under conditions such as those described hereinbefore in
 respect of process step (ii) above;
- 15 (xiv) for compounds of formula I in which X^1 represents $-N(R^9)-J-R^{10}$, reaction of
 a compound of formula XV,



- 20 wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^9 are as hereinbefore defined, with a
 compound of formula XVI,



- wherein J, R¹⁰ and L¹ are as hereinbefore defined, for example at around room temperature or above (e.g. up to 60-70°C) in the presence of a suitable base (e.g. pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene,
5 sodium hydroxide, or mixtures thereof), an appropriate solvent (e.g. pyridine, dichloromethane, chloroform, tetrahydrofuran, dimethylformamide, triethylamine, dimethylsulfoxide, water or mixtures thereof) and, in the case of biphasic reaction conditions, optionally in the presence of a phase transfer catalyst;
- 10 (xv) for compounds of formula I in which X¹ represents -N(R⁹)-J-R¹⁰, J represents a single bond and R¹⁰ represents a C₁₋₈ alkyl group, reduction of a corresponding compound of formula I, in which J represents -C(O)- and R¹⁰ represents H or a C₁₋₇ alkyl group, in the presence of a suitable reducing agent. A suitable reducing agent may be an appropriate reagent that reduces the amide group to the amine
15 group in the presence of other functional groups (for example an ester or a carboxylic acid). Suitable reducing agents include borane and other reagents known to the skilled person;
- (xvi) for compounds of formula I in which X¹ represents halo, reaction of a
20 compound of formula I wherein X¹ represents H, with a reagent or mixture of reagents known to be a source of halide atoms. For example, for bromide atoms, *N*-bromosuccinimide, bromine or 1,2-dibromotetrachloroethane may be employed, for iodide atoms, iodine, diiodoethane, diiodotetrachloroethane or a mixture of NaI or KI and *N*-chlorosuccinimide may be employed, for chloride atoms, *N*-
25 chlorosuccinimide may be employed and for fluoride atoms, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), 1-fluoropyridinium triflate, xenon difluoride, CF₃OF or perchloryl fluoride may be employed. This reaction may be carried out in a suitable solvent (e.g. acetone, benzene or dioxane) under conditions known to the skilled person;
- 30 (xvii) for compounds of formula I in which R⁶ is other than H, reaction of a compound of formula XVII,



wherein L^5 represents an appropriate alkali metal group (e.g. sodium, potassium
 5 or, especially, lithium), a -Mg-halide, a zinc-based group or a suitable leaving
 group such as halo or $-B(OH)_2$, or a protected derivative thereof (the skilled
 person will appreciate that the compound of formula XVII in which L^5 represents
 an alkali metal (e.g. lithium), a Mg-halide or a zinc-based group may be prepared
 from a corresponding compound of formula XVII in which L^5 represents halo, for
 10 example under conditions such as those hereinbefore described in respect of
 preparation of compounds of formula I (process step (x) above)), and X^1 , R^1 , R^2 ,
 R^3 , R^4 and R^5 are as hereinbefore defined, with a compound of formula XVIII,



15 wherein R^{6a} represents R^6 provided that it does not represent H, and L^6 represents
 a suitable leaving group such as halo (especially chloro or bromo) under
 conditions known to those skilled in the art. The skilled person will appreciate
 that L^5 and L^6 (when they both represent leaving groups) will be mutually
 20 compatible in a similar manner to the L^1 and L^2 groups described hereinbefore in
 process step (ii) above;

(xviii) for compounds of formula I in which R^6 is H, reaction of a compound of
 formula XVII in which L^5 represents either:

- 25 (I) an alkali metal (for example, such as one defined in respect of process
 step (xvii) above); or
 (II) -Mg-halide,

with carbon dioxide, followed by acidification under standard conditions known to
 those skilled in the art, for example, in the presence of aqueous hydrochloric acid;

(xix) reaction of a corresponding compound of formula XVII in which L^5 is a suitable leaving group known to those skilled in the art (such as a sulfonate group (e.g. a triflate) or, preferably, a halo (e.g. bromo or iodo) group) with CO (or a reagent that is a suitable source of CO (e.g. $Mo(CO)_6$ or $Co_2(CO)_8$)), in the presence of a compound of formula XIX,



XIX

wherein R^6 is as hereinbefore defined, and an appropriate catalyst system (e.g. a palladium catalyst such as one described hereinbefore in respect of process step (ii)) under conditions known to those skilled in the art;

(xx) for compounds of formula I in which R^6 represents H, hydrolysis of a corresponding compound of formula I in which R^6 does not represent H under standard conditions;

(xxi) for compounds of formula I in which R^6 does not represent H:

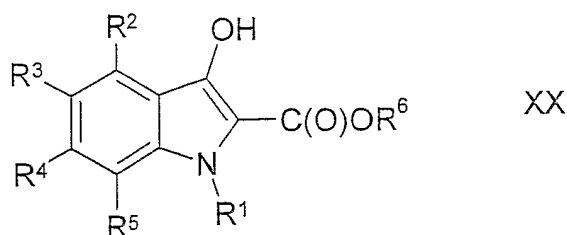
(A) esterification of a corresponding compound of formula I in which R^6 represents H; or

(B) trans-esterification of a corresponding compound of formula I in which R^6 does not represent H (and does not represent the same value of R^6 as the compound of formula I to be prepared),

under standard conditions in the presence of the appropriate alcohol of formula XIX as hereinbefore defined but in which R^6 represents R^{6a} ;

(xxii) for compounds of formula I in which X^1 represents $-Q-X^2$ in which Q represents $-O-$, reaction of a compound of formula XX,

39



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

5



wherein L^7 represents a suitable leaving group, such as a halo or sulfonate group and X^2 is as hereinbefore defined, for example in the presence of a base or under reaction conditions such as those described hereinbefore in respect of process (xiii) above;

(xxiii) for compounds of formula I in which X^1 represents $-N(R^9)-J-R^{10}$, reaction of a compound of formula XX as hereinbefore defined, with a compound of formula VI in which X^{1b} represents $-N(R^9)-J-R^{10}$ and R^9 , R^{10} and J are as hereinbefore defined, for example under reaction conditions known to those skilled in the art (such as those described in *Journal of Medicinal Chemistry* 1996, Vol. 39, 4044 (e.g. in the presence of $MgCl_2$));

(xxiv) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl substituted α to the indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, reaction of a corresponding compound of formula I in which X^1 represents H with a compound corresponding to a compound of formula VI, but in which X^{1b} represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which groups are substituted by a Z^1 group in which Z^1 represents $=O$, under conditions known to those skilled in the art, for example optionally in the presence of an acid, such as a protic acid or an appropriate Lewis acid. Such substitutions

are described in *inter alia* *Bioorg. Med. Chem. Lett.*, **14**, 4741-4745 (2004) and *Tetrahedron Lett.* **34**, 1529 (1993);

(xxv) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a
5 single bond and X^2 represents C_{2-8} alkyl substituted (e.g. α to the indole ring) by a
 G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5$, A^5 represents
a single bond and R^{11a} represents H, reaction of a corresponding compound of
formula I in which X^2 represents C_{1-7} alkyl substituted (e.g. α to the indole ring)
by a Z^1 group in which Z^1 represents $=O$, with the corresponding Grignard reagent
10 derivative of a compound of formula V in which L^2 represents chloro, bromo or
iodo, Q^a is a single bond and X^2 represents C_{1-7} alkyl, under conditions known to
those skilled in the art;

(xxvi) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a
15 single bond, and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which are
unsubstituted in the position α to the indole ring, reduction of a corresponding
compound of formula I in which X^2 represents C_{1-8} alkyl substituted α to the
indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents
 $-OA^5$, A^5 represents a single bond and R^{11a} represents H, in the presence of a
20 suitable reducing agent such as a mixture of triethyl silane and a protic acid (e.g.
 CF_3COOH) or a Lewis acid (e.g. $(CH_3)_3SiOS(O)_2CF_3$) for example under
conditions described in *inter alia* *Bioorg. Med. Chem. Lett.*, **14**, 4741-4745
(2004);

(xxvii) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a
25 single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, neither of which are
substituted by Z^1 in which Z^1 represents $=O$, reduction of a corresponding
compound of formula I in which X^2 represents C_{1-8} alkyl or heterocycloalkyl,
which groups are substituted by one or more Z^1 groups in which Z^1 represents $=O$
30 under conditions known to those skilled in the art, for example employing $NaBH_4$
in the presence of an acid (e.g. CH_3COOH or CF_3COOH), Wolff-Kishner
reduction conditions (i.e. by conversion of the carbonyl group to a hydrazone,

followed by base induced elimination) or by conversion of the carbonyl to the thioacetal analogue (e.g. by reaction with a dithiane) followed by reduction with e.g. Raney nickel, all under reaction conditions known to those skilled in the art; or

5

(xxviii) for compounds of formula I in which one of the groups R^2 , R^3 , R^4 or R^5 represents a heterocycloalkyl group linked to the benzenoid moiety of the indole ring by a nitrogen atom, reaction of a compound of formula X as hereinbefore defined with a compound of formula XXIA,

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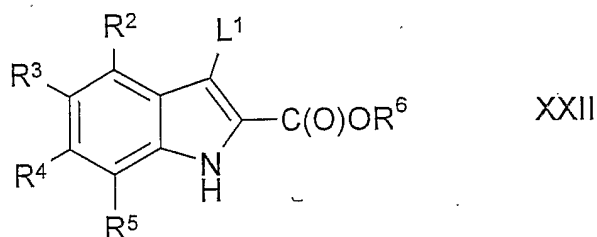
wherein (R^{2y-5y}) represents R^{2-5} as hereinbefore defined provided that the appropriate R^2 , R^3 , R^4 or R^5 substituent represents a heterocycloalkyl group in which the hydrogen atom of the compound of formula XXIA is attached to a nitrogen atom of that group, for example under similar conditions to those described hereinbefore in respect of processes (i) and/or (ii) above.

15

Compounds of formula II may be prepared by:

20

(a) reaction of a compound of formula XXII,



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wherein L^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as hereinbefore defined, with, for compounds of formula II in which X^1 represents:

(1) $-Q-X^2$ and Q represents a single bond or $-C(O)-$, a compound of formula V as hereinbefore defined; or

(2) $-N(R^9)-J-R^{10}$ or $-Q-X^2$, in which Q represents $-O-$ or $-S-$, a compound of formula VI as hereinbefore defined;

for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (processes (ii) and (iv), respectively) above;

5

(b) for compounds of formula II in which X^1 represents $-Q-X^2$ and Q represents $-C(O)-$, reaction of a corresponding compound of formula II in which X^1 represents H with a compound of formula V in which Q^a represents $-C(O)-$ and L^2 represents a suitable leaving group, for example under conditions such as those described in respect of preparation of compounds of formula I (process (iii)) above.

10

(c) for compounds of formula II in which X^1 represents $-Q-X^2$ and Q represents $-S-$, reaction of a compound of formula II in which X^1 represents H with a compound of formula VI in which X^{1b} represents $-Q-X^2$ and Q represents $-S-$, for example under conditions such as those described hereinbefore in respect of preparation of compounds of formula I (process (v)) above;

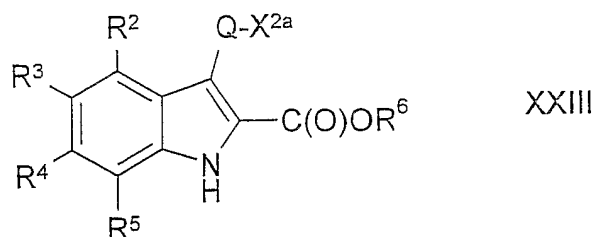
20

(d) for compounds of formula II in which X^1 represent $-Q-X^2$ and Q represents $-S(O)-$ or $-S(O)_2-$, oxidation a corresponding compound of formula II in which Q represent $-S-$;

25

(e) for compounds of formula II in which X^1 represents $-Q-X^2$, X^2 represents C_{1-8} alkyl substituted by G^1 , G^1 represents $-A^1-R^{11a}$, A^1 represents $-N(R^{12a})A^4-$ and A^4 is a single bond (provided that Q represents a single bond when X^2 represents substituted C_1 alkyl), reaction of a compound of formula XXIII,

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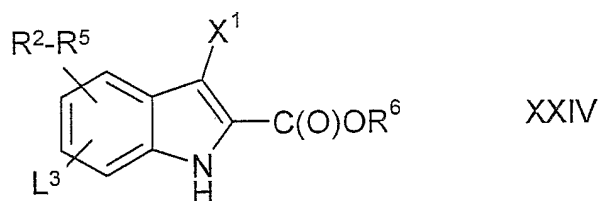
wherein Q, X^{2a}, R², R³, R⁴, R⁵ and R⁶ are as hereinbefore defined by reductive amination in the presence of a compound of formula VIII as hereinbefore defined;

(ea) for compounds of formula II in which X¹ represents -Q-X², Q represents a single bond, X² represents methyl substituted by G¹, G¹ represents -A¹-R^{11a}, A¹ represents -N(R^{12a})A⁴-, A⁴ is a single bond and R^{11a} and R^{12a} are preferably methyl, reaction of a corresponding compound of formula II in which X¹ represents H, with a mixture of formaldehyde (or equivalent reagent) and a compound of formula VIII as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (viiia)) above;

(f) for compounds of formula II in which X¹ represents -Q-X², Q represents a single bond and X² represents optionally substituted C₂₋₈ alkenyl (in which a point of unsaturation is between the carbon atoms that are α and β to the indole ring), reaction of a corresponding compound of formula XXII in which L¹ represents halo (e.g. iodo) with a compound of formula IXA as hereinbefore defined, or reaction of a compound of formula XXIII in which Q represents a single bond and X^{2a} represents -CHO with a compound of formula IXB or a compound of formula IXC as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (viii)) above;

(g) for compounds of formula II in which X^1 represents $-Q-X^2$ and X^2 represents optionally substituted, saturated C_{2-8} alkyl, saturated cycloalkyl, saturated heterocycloalkyl, C_{2-8} alkenyl, cycloalkenyl or heterocycloalkenyl, reduction (e.g. hydrogenation) of a corresponding compound of formula II in which X^2 represents optionally substituted C_{2-8} alkenyl, cycloalkenyl, heterocycloalkenyl, C_{2-8} alkynyl, cycloalkynyl or heterocycloalkynyl (as appropriate);

(h) for compounds of formula II in which one or more of R^2 to R^5 represents $-D-E$ and D represents $-C(O)-$, $-C(R^7)(R^8)-$, C_{2-8} alkylene or $-S(O)_2-$, or optionally substituted cycloalkyl or heterocycloalkyl, reaction of a compound of formula XXIV,

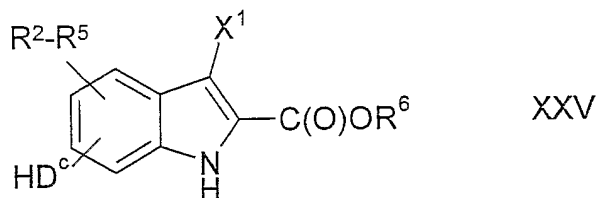


wherein X^1 , L^3 , R^2-R^5 and R^6 are as hereinbefore defined with a compound of formula XI or XIA (as appropriate) as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (x)) above;

(i) for compounds of formula II in which when one of R^2 to R^5 represents $-D-E-$ and D represents $-S-$, $-O-$ or C_{2-4} alkynylene in which the triple bond is adjacent to E , reaction of a compound of formula XXIV as hereinbefore defined in which L^3 represents L^2 as hereinbefore defined (for example $-B(OH)_2$) with a compound of formula XII as hereinbefore defined, for example under reaction

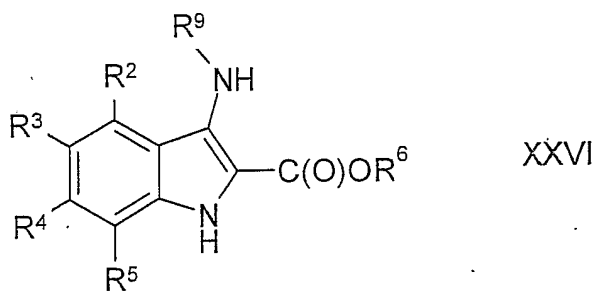
conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xi)) above;

- (j) for compounds of formula II in which when one of R^2 to R^5 represents -D-E- and D represents -S(O)- or -S(O)₂-, oxidation of a corresponding compound of formula II in which D represents -S-;
- (k) for compounds of formula II in which when one of R^2 to R^5 represents -D-E- and D represents -O- or -S-, reaction of a compound of formula XXV,



wherein D^c , X^1 , R^2 - R^5 and R^6 are as hereinbefore defined, with a compound of formula XIV as hereinbefore defined;

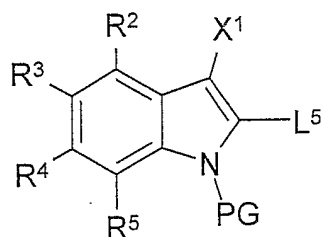
- (l) for compounds of formula II in which X^1 represents -N(R^9)-J- R^{10} , reaction of a compound of formula XXVI,



wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^9 are as hereinbefore defined with a compound of formula XVI as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in

respect of preparation of compounds of formula I (process (xiv)) above;

- 5 (m) for compounds of formula II in which X^1 represents $-N(R^9)-J-R^{10}$, J represents a single bond and R^{10} represents a C_{1-8} alkyl group, reduction of a corresponding compound of formula II, in which J represents $-C(O)-$ and R^{10} represents H or a C_{1-7} alkyl group, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of
- 10 formula I (process (xv)) above;
- (n) for compounds of formula II in which X^1 represents halo, reaction of a compound of formula II wherein X^1 represents H, with a reagent or mixture of reagents known to be a source of halide
- 15 atoms, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xvi)) above;
- (o) for compounds of formula II in which R^6 is other than H, reaction
- 20 of a compound of formula XXVII,

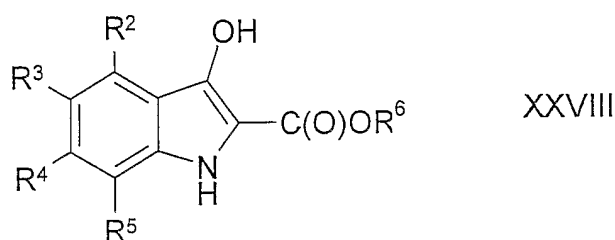


XXVII

- 25 wherein PG represents a suitable protecting group (such as $-S(O)_2Ph$, $-C(O)O^-$, $-C(O)OtBu$ or $-C(O)N(Et)_2$) and L^5 , X^1 , R^2 , R^3 , R^4 and R^5 are as hereinbefore defined, with a compound of formula XVIII as hereinbefore defined, or a protected derivative thereof, for example under similar coupling conditions to those described

hereinbefore in respect of process (xvii) above, followed by deprotection of the resultant compound under standard conditions;

- 5 (p) for compounds of formula II in which R^6 is H, reaction of a compound of formula XXVII in which L^5 represents an alkali metal, or -Mg-halide, with carbon dioxide, followed by acidification;
- 10 (q) reaction of a corresponding compound of formula XXVII in which L^5 is a suitable leaving group known to those skilled in the art (such as a halo (e.g. bromo or iodo) group) with CO (or a reagent that is a suitable source of CO), in the presence of a compound of formula XIX as hereinbefore defined;
- 15 (r) for compounds of formula II in which R^6 represents H, hydrolysis of a corresponding compound of formula II in which R^6 does not represent H;
- 20 (s) for compounds of formula II in which R^6 does not represent H:
 (A) esterification of a corresponding compound of formula II in which R^6 represents H; or
 (B) trans-esterification of a corresponding compound of formula II in which R^6 does not represent H (and does not represent the same value of R^6 as the compound of formula II to be prepared);
- 25 (t) for compounds of formula II in which X^1 represents -Q- X^2 in which Q represents -O-, reaction of a compound of formula XXVIII,



wherein R^2 , R^3 , R^4 , R^5 and R^6 are as hereinbefore defined, with a compound of formula XXI as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxii)) above;

5 (u) for compounds of formula II in which X^1 represents $-N(R^9)-J-R^{10}$, reaction of a compound of formula XXVIII as hereinbefore defined, with a compound of formula VI in which X^{1b} represents $-N(R^9)-J-R^{10}$ and R^9 , R^{10} and J are as hereinbefore defined, for example under conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxiii)) above;

15 (v) for compounds of formula II in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl substituted α to the indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, reaction of a corresponding compound of formula II in which X^1 represents H with a compound corresponding to a compound of formula VI, but in which X^{1b} represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which groups are substituted by a Z^1 group in which Z^1 represents $=O$, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxiv)) above;

20 25 30 (w) for compounds of formula II in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{2-8} alkyl substituted (e.g. α to the indole ring) by a G^1 substituent in which G^1 represents

- 5 $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, reaction of a corresponding compound of formula II in which X^2 represents C_{1-7} alkyl substituted (e.g. α to the indole ring) by a Z^1 group in which Z^1 represents $=O$, with the corresponding Grignard reagent derivative of a compound of formula V in which L^2 represents chloro, bromo or iodo, Q^a is a single bond and X^2 represents C_{1-7} alkyl, under conditions known to those skilled in the art;
- 10 (x) for compounds of formula II in which X^1 represents $-Q-X^2$, Q represents a single bond, and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which are unsubstituted in the position α to the indole ring, reduction of a corresponding compound of formula II in which X^2 represents C_{1-8} alkyl substituted α to the
- 15 indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxvi)) above;
- 20 (y) for compounds of formula II in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, neither of which are substituted by Z^1 in which Z^1 represents $=O$, reduction of a corresponding compound of formula
- 25 II in which X^2 represents C_{1-8} alkyl or heterocycloalkyl, which groups are substituted by one or more Z^1 groups in which Z^1 represents $=O$, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxvii)) above; or
- 30 (z) for compounds of formula II in which one of the groups R^2 , R^3 , R^4 or R^5 represents a heterocycloalkyl group linked to the benzenoid

moiety of the indole ring by a nitrogen atom, reaction of a compound of formula XXIV as hereinbefore defined (or a protected derivative thereof) with a compound of formula XXIA as hereinbefore defined, for example under similar conditions to those hereinbefore described in respect of preparation of compounds of formula I (process (xxviii)) above.

Compounds of formula IV may be prepared as follows:

- (a) Reaction of a compound of formula XXII as hereinbefore defined with a compound of formula XXIX,

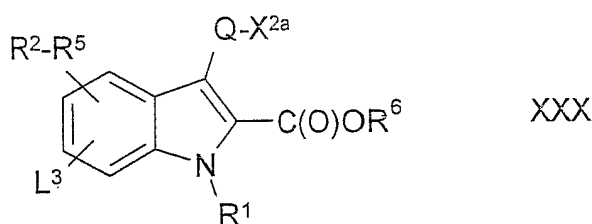


wherein R^1 and L^2 are as hereinbefore defined or a compound of formula III as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (processes (ii) and (i), respectively) above; or

- (b) for compounds of formula IV wherein L^1 represents a sulfonate group, reaction of a compound of formula XX 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 VII may be prepared by:

- (a) for compounds of formula VII in which one of R^2 to R^5 represents -D-E and D represents -C(O)-, -C(R^7)(R^8)-, C_{2-8} alkylene or -S(O)₂-, or optionally substituted cycloalkyl or heterocycloalkyl, reaction of a compound of formula XXX,



5 wherein Q, X^{2a}, L³, R¹, R²-R⁵ and R⁶ are as hereinbefore defined (L³ in particular may represent halo, such as bromo) with a compound of formula XI or XIA (as appropriate) as hereinbefore defined (in which L⁴ may in particular represent -B(OH)₂), for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (x)) above;

10

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

15

(c) for compounds of formula VII in which Q represents a single bond and X^{2a} represents -CHO, reaction of a corresponding compound of formula I in which X¹ represents H with a mixture of DMF and, for example, oxalyl chloride, phosgene or P(O)Cl₃ (or the like) in an appropriate solvent system (e.g. DMF or dichloromethane).

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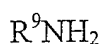
Compounds of formula X may be prepared by reaction of a compound of formula XXIV as hereinbefore defined, with a compound of formula III as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (i)) above.

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Compounds of formula X in which L³ represents L² may be prepared by reaction of a compound of formula X in which L³ represents L¹, with an appropriate

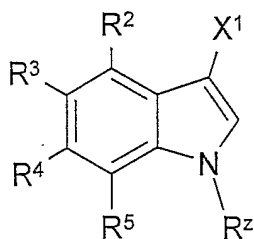
reagent for the conversion of the L^1 group to the L^2 group. This conversion may be performed by methods known to those skilled in the art, for example, compounds of formula X, in which L^3 is 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl may be prepared by reaction of the reagent bis(pinacolato)diboron with a compound of formula X in which L^3 represents L^1 , for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (ii)) above).

Compounds of formulae XV and XXVI may be prepared by reaction of a corresponding compound of formula IV, or XXII, respectively, with a compound of formula XXXI,



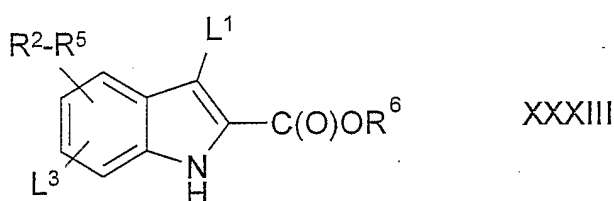
wherein R^9 is as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (ii)) above).

Compounds of formula XVII and XXVII in which L^5 represents an appropriate alkali metal, such as lithium may be prepared by reaction of a compound of formula XXXII,



wherein R^Z represents R^1 (in the case of a compound of formula XVII) or PG (in the case of a compound of formula XXVII), and PG, X^1 , R^1 , R^2 , R^3 , R^4 and R^5 are as hereinbefore defined, with an appropriate base, such lithium diisopropylamide or BuLi under standard conditions. Compounds of formulae XVII and XXVII in which L^5 represents -Mg-halide may be prepared from a corresponding compound

- of formula XVII or XXVII (as appropriate) in which L^5 represents halo, for example under conditions such as those described hereinbefore in respect of process step (x). Compounds of formulae XVII and XXVII in which L^5 represents, for example, a zinc-based group, or a halo or boronic acid group, may be prepared by reacting a corresponding compound of formula XVII or XXVII in which L^5 represents an alkali metal with an appropriate reagent for introduction of the relevant group, for example by a metal exchange reaction (e.g. a Zn transmetallation), by reaction with a suitable reagent for the introduction of a halo group (for example, a reagent described hereinbefore in respect of preparation of compounds of formula I (process (xvi)) or, for the introduction of a boronic acid group, 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.
- Compounds of formula XXII may be prepared by standard techniques. For example, compounds of formula XXII in which one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group, or in which one of R^2 to R^5 represents -D-E and D represents -C(O)-, -C(R^7)(R^8)-, C_{2-4} alkylene or -S(O)₂-, may be prepared by reaction of a compound of formula XXXIII,



- wherein L^1 , L^3 , R^2 - R^5 and R^6 are as hereinbefore defined with a compound of formula XI (when one of R^2 to R^5 represents -D-E and D represents -C(O)-, -C(R^7)(R^8)-, C_{2-4} alkylene or -S(O)₂-) or XIA or XXIA (when one of R^2 to R^5 represents optionally substituted cycloalkyl or heterocycloalkyl) as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (x)) above.

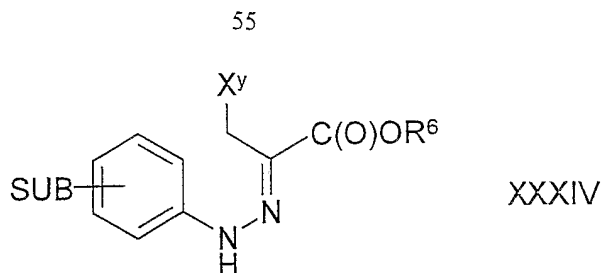
Compounds of formulae XXIII and XXX, in which Q represents a single bond and X^{2a} represents -CHO, may be prepared from compounds of formulae II, or X, respectively, in which X^1 represents H, by reaction with a mixture of DMF and,
5 for example, oxalyl chloride, phosgene or $P(O)Cl_3$ (or the like) in an appropriate solvent system (e.g. DMF or dichloromethane) for example as described hereinbefore.

Compounds of formulae III, V, VI, VIII, IXA, IXB, IXC, XI, XIA, XII, XIII,
10 XIV, XVI, XVIII, XIX, XX, XXI, XXIA, XXIV, XXV, XXVIII, XXIX, XXXI, XXXII and XXXIII 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
15 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, VII, X, XIII, XV, XVII, XX, XXII, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII, XXX, XXXII and XXXIII may also be prepared
20 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.

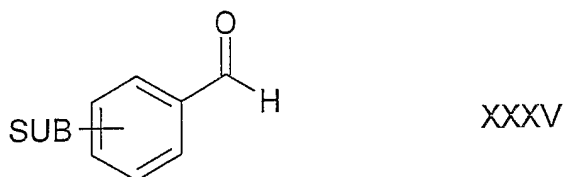
25

For example, compounds of formulae II, XXIV and XXV, in which X^1 represents H, $-N(R^9)-J-R^{10}$ or $-Q-X^2$, may be prepared by reaction of a compound of formula XXXIV,



wherein SUB represents the substitution pattern that is present in the relevant compound to be formed (in this case, the compound of formula II, XXIV or XXV; respectively), X^y represents H, $-N(R^9)-J-R^{10}$ or $-Q-X^2$, and R^6 , R^9 , R^{10} , J, X^2 and Q are as hereinbefore defined, under Fischer indole synthesis conditions known to the person skilled in the art.

Compounds of formulae II, XXIV and XXV in which X^1 represents H may be prepared by reaction of a compound of formula XXXV,



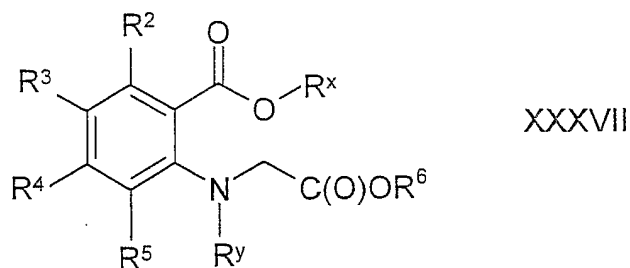
wherein SUB is as hereinbefore defined with a compound of formula XXXVI,



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).

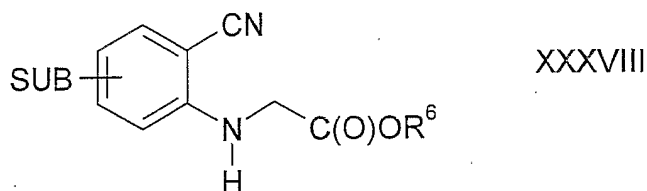
Compounds of formulae XX and XXVIII may be prepared by reaction of a compound of formula XXXVII,

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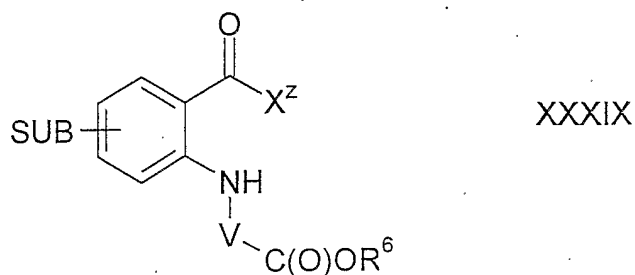
wherein R^x represents a C₁₋₆ alkyl group, R^y represents either R¹ (as required for the formation of compounds of formula XX), hydrogen (as required for the formation of compounds of formula XXVIII) or a nitrogen-protected derivative thereof, and R¹, R², R³, R⁴, R⁵ and R⁶ are as hereinbefore defined for example under cyclisation conditions known to those skilled in the art.

Compounds of formulae II, XXIV and XXV in which X¹ represents -NH₂, may be prepared by reaction of a compound of formula XXXVIII,



wherein SUB and R⁶ are as hereinbefore defined, for example under intramolecular cyclisation conditions known to those skilled in the art.

Compounds of formulae II and XXIV in which X¹ represents H, -N(R⁹)-J-R¹⁰ or -Q-X² in which Q represents a single bond or -C(O)-, may alternatively be prepared by reaction of a compound of formula XXXIX,

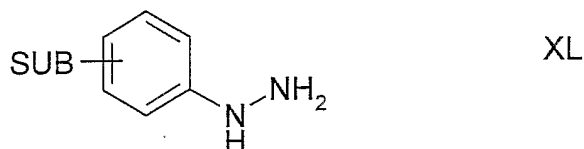


wherein V represents either -C(O)- or -CH₂-, X² represents H, -N(R⁹)-J-R¹⁰ or -Q-X² in which Q represents a single bond or -C(O)- and SUB, R⁹, R¹⁰, J, X² and R⁶ are as hereinbefore defined. When V represents -C(O)-, the intramolecular cyclisation may be induced by a reducing agent such as TiCl₃/C₈K, TiCl₄/Zn or SmI₂ under conditions known to the skilled person, for example, at room temperature in the presence of a polar aprotic solvent (such as THF). When V represents -CH₂-, the reaction may be performed in the presence of base under intramolecular condensation reaction conditions known to the skilled person.

10

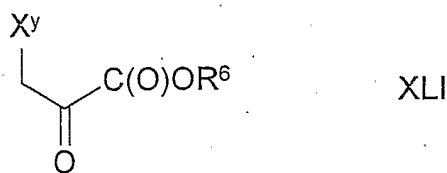
Compounds of formula XXXIV may be prepared by:

- (a) reaction of a compound of formula XL,



15

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



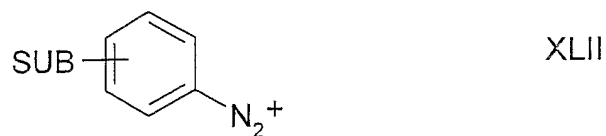
20

wherein X^y and R⁶ are as hereinbefore defined under condensation conditions known to the skilled person; or

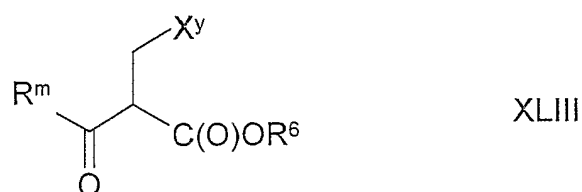
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- (b) reaction of a compound of formula XLII,

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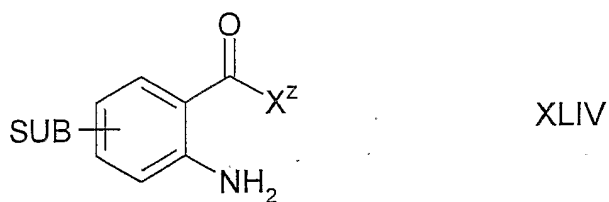


wherein SUB is as hereinbefore defined with a compound of formula XLIII,

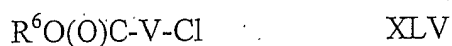


wherein R^m represents OH, O-C₁₋₆ alkyl or C₁₋₆ alkyl and X^y and R⁶ are as hereinbefore defined, for example under Japp-Klingemann conditions known to the skilled person.

Compounds of formula XXXIX may be prepared by reaction of a compound of XLIV,



wherein SUB and X^z are as hereinbefore defined with a compound of formula XLV,



wherein R⁶ and V are as hereinbefore defined, under standard coupling conditions.

Compounds of formulae XXXV, XXXVI, XXXVII, XXXVIII, XL, XLI, XLII, XLIII, XLIV and XLV 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.

- 10 The substituents X^1 , 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, acylations, 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.
- 20
- 25 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.
- 30

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, as hereinbefore defined but without provisos (b) and (d), 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
5 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
10 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
15 “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
20 parenteral administration to form compounds which possess pharmacological activity.

Compounds of the invention are particularly useful because they may inhibit the activity of a member of the MAPEG family.
25

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
30 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 C₄ (LTC₄), for
5 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 LTC₄ 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
10 (1992).

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

15 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
20 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.

25 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,
30 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 asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory bowel disease, irritable bowel syndrome, inflammatory pain, fever, migraine, headache, low back pain, fibromyalgia, myofascial disorders, viral infections (*e.g.* influenza, common cold, herpes zoster, hepatitis C and AIDS), bacterial infections, fungal infections, dysmenorrhea, burns, surgical or dental procedures, malignancies (*e.g.* breast cancer, colon cancer, and prostate cancer), hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, 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, allergic disorders, rhinitis, ulcers, coronary heart disease, sarcoidosis and any other disease with an inflammatory component.

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, a member of the MAPEG family such as a PGES (*e.g.* mPGES-1), LTC₄ and/or FLAP and/or a method of treatment of a disease in which inhibition of the activity of a member of the MAPEG family such as PGES (and

particularly mPGES-1), LTC₄ and/or FLAP 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 but without the provisos, 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 but without provisos (b) and (d), 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 but without the provisos; 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 but without the provisos, 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 but without the provisos, 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,

5 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
10 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.
15 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
20 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
25 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 a member of MAPEG family, e.g. inhibitors of
30 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 PGE₂ 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 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 mPGES-1 is dissolved in 0,1M KPi-buffer pH 7,35 with 2,5mM 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 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:

5	BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
	Boc	<i>tert</i> -butoxycarbonyl
	cy	cyclohexyl
	dba	dibenzylideneacetone
	DIBAL	diisobutylaluminium hydride
10	DMAP	4,4-dimethylaminopyridine
	DMF	dimethylformamide
	DMSO	dimethylsulfoxide
	DPEphos	bis-(2-diphenylphosphinophenyl)ether
	EtOAc	ethyl acetate
15	HPLC	High Pressure Liquid Chromatography
	MeCN	acetonitrile
	MS	mass spectrum
	NBS	<i>N</i> -bromosuccinimide
	NMR	nuclear magnetic resonance
20	rt	room temperature
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
	xantphos	9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene

25

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

Example 15-(3-Isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid(a) 5-Benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl5 ester

An oven-dried vial (4 mL) was charged with K_3PO_4 (220 mg, 1.05 mmol), 5-benzyloxyindole-2-carboxylic acid ethyl ester (150 mg, 0.5 mmol) and flushed with argon. A solution of 4-isopropoxyphenyl bromide (150 mg, 0.7 mmol) in toluene (1.0 mL) was added, followed by a solution of CuI (22.9 mg, 0.12 mmol) and *N,N*-dimethyl-1,2-diaminoethane (25.5 μ L, 0.24 mmol) in toluene (1.2 mL). The mixture was heated at 110 °C for 20 h, cooled and filtered. The solids were washed with acetone and the combined filtrates concentrated and purified by chromatography affording the sub-title compound (163 mg, 75%).

15 (b) 5-Hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (1.00 g, 2.3 mmol; see step (a) above), HCl (aq, conc, 0.42 mL) and EtOAc (15 mL) was hydrogenated at ambient temperature and pressure over 10% Pd on carbon (0.45 g) for 1.5 h. The mixture was filtered, the filtrate concentrated and the residue purified by chromatography to give the sub-title compound (0.70 g, 88%).

(c) 5-(3-Isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

25 Anhydrous CH_2Cl_2 (6 mL), Et_3N (164 μ L, 1.18 mmol) and pyridine (93 mg, 1.18 mmol) were added to 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.59 mmol; see step (b) above), $Cu(OAc)_2$ (107 mg, 0.59 mmol) and 3-isopropoxyphenylboronic acid (212 mg, 1.18 mmol). The mixture was stirred vigorously at rt for 24 h. After the reaction was complete (as judged by TLC), the mixture was filtered through Celite[®], concentrated and purified by chromatography to give the sub-title compound (141 mg, 51%).

(d) 5-(3-Isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

A mixture of 5-(3-isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (141 mg, 0.30 mmol; see step (c) above), dioxane (3.8 mL) and NaOH (aq, 2 M, 3.0 mL) was heated by microwave irradiation at 120 °C for 15 min. After cooling to rt the mixture was diluted with brine, neutralized to pH 2 by with HCl (aq, 1 M) and extracted with EtOAc. Concentration of the combined extracts and purification by chromatography gave the title compound (120 mg, 91%).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.32-7.11 (4H, m) 7.07-6.90 (3H, m) 6.87-6.71 (2H, m) 6.59 (1H, d, *J* = 8.8 Hz) 6.50-6.38 (2H, m) 6.36-6.28 (1H, m) 4.75-4.50 (2H, m) 1.33 (6H, d, *J* = 6.2 Hz) 1.24 (6H, d, *J* = 6.2 Hz).

Example 2

5-(2-Isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 2-isopropoxyphenylboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.28-7.16 (2H, m) 7.15-7.05 (4H, m) 7.04-6.86 (6H, m) 4.72-4.50 (2H, m) 1.31 (6H, d, *J* = 6.0 Hz) 1.16 (6H, d, *J* = 6.0 Hz).

Example 3

5-(4-Isopropoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-isopropoxyphenylboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.20-7.08 (3H, m) 7.01-6.74 (10H, m) 4.70-4.42 (2H, m) 1.31 (6H, d, *J* = 6.2 Hz) 1.24 (6H, d, *J* = 6.2 Hz).

Example 41-(4-Isopropoxyphenyl)-5-(3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3-trifluoromethoxyphenylboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.43 (1H, t, *J* = 8.6 Hz) 7.29 (1H, d, *J* = 2.2 Hz) 7.18 (1H, d, *J* = 8.6 Hz) 7.06-6.92 (5H, m) 6.91-6.79 (3H, m) 6.74 (1H, s) 4.64 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz)

10 Example 55-(4-Trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-trifluoromethoxyphenylboronic acid.

15 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.1-12.4 (1H, br s) 7.45-7.39 (1H, m) 7.37-7.19 (5H, m) 7.08-6.96 (6H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz).

Example 620 5-(3,5-Dichlorophenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3,5-dichlorophenylboronic acid.

25 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.9-12.7 (1H, br s) 7.53-7.49 (1H, m) 7.33 (1H, s) 7.32-7.29 (2H, m) 7.25 (1H, s) 7.10-7.02 (3H, m) 7.01-6.93 (3H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz).

Example 75-(3-Chlorophenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

30 The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3-chlorophenylboronic acid.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.40-7.30 (2H, m) 7.28-7.08 (4H, m) 7.06-6.86 (6H, m) 4.68 (1H, septet, $J = 6.0$ Hz) 1.32 (6H, d, $J = 6.0$ Hz).

Example 8

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

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-*tert*-butylphenylboronic acid.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.2-12.5 (1H, br s) 7.38-7.21 (6H, m)
10 7.03-6.98 (4H, m) 6.88 (2H, d, $J = 8.6$ Hz) 4.68 (1H, septet, $J = 6.0$ Hz) 1.34 (6H, d, $J = 6.0$ Hz) 1.27 (9H, s).

Example 9

15 1-(4-Isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid hemihydrate

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-trifluoromethylphenylboronic acid.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.2-12.6 (1H, br s) 7.72 (2H, d, $J = 8.7$
20 Hz) 7.53-7.48 (1H, m) 7.35-7.24 (3H, m) 7.14-7.00 (6H, m) 4.69 (1H, septet, $J = 6.0$ Hz) 1.35 (6H, d, $J = 6.0$ Hz).

Example 10

5-(4-Chlorophenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

25 The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-chlorophenylboronic acid.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.2-12.3 (1H, br s) 7.42-7.35 (3H, m)
7.30-7.22 (3H, m) 7.07-6.92 (6H, m) 4.67 (1H, septet, $J = 6.2$ Hz) 1.33 (6H, d, J
30 = 6.2 Hz).

Example 115-(3,4-Dichlorophenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3,4-dichlorophenylboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.55 (1H, d, *J* = 8.4 Hz) 7.38-7.11 (4H, m) 7.06-6.69 (6H, m) 4.64 (1H, septet, *J* = 6.2 Hz) 1.31 (6H, d, *J* = 6.2 Hz).

Example 12

10 1-(4-Isopropoxyphenyl)-5-(3-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3-trifluoromethylphenylboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.64-7.52 (1H, m) 7.50-7.38 (2H, m) 7.35-15 7.20 (5H, m) 7.10-6.98 (4H, m) 4.68 (1H, septet, *J* = 5.9 Hz) 1.34 (6H, d, *J* = 5.9 Hz).

Example 131-(4-Isopropoxyphenyl)-5-(quinolin-3-yloxy)indole-2-carboxylic acid

20 The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 3-quinolineboronic acid.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 8.45-8.43 (1H, m) 8.00 (1H, d, *J* = 8.2 Hz) 7.85 (1H, d, *J* = 8.2 Hz) 7.71-7.46 (3H, m) 7.37 (1H, d, *J* = 1.7 Hz) 7.19 (2H, d, *J* = 8.6 Hz) 7.10-6.86 (4H, m) 6.78-6.72 (1H, m) 4.70-4.45 (1H, m) 1.32 (6H, d, *J* = 25 6.0 Hz)

Example 145-(4-Chloro-3-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid5 (a) 4-Bromo-1-chloro-2-trifluoromethoxybenzene

NaNO₂ (2.43 g, 0.035 mol) in water (10 mL) was added in portions over 30 min to 4-bromo-2-trifluoromethoxyaniline (9 g, 35 mmol) in a mixture of HCl (aq, conc, 25 mL) and water (25 mL) at (0–2 °C). The mixture was stirred at 0–2 °C for 15 min and CuCl (6 g, 61 mmol) in HCl (aq, conc, 10 mL) was added dropwise. After 10 min at rt, the mixture was heated at reflux for 15 min. Steam-distillation followed by extraction (CH₂Cl₂), drying (Na₂SO₄) of the distillate followed by concentration and distillation (bp 82–84 °C at 20 Torr) gave 3.86 g (40%) of the sub-title compound.

15 (b) 4-Chloro-3-trifluoromethoxyphenylboronic acid

n-BuLi (2.5 M in hexanes; 6.25 mL, 12.5 mmol) was added dropwise to 4-bromo-1-chloro-2-trifluoromethoxybenzene (3.4 g, 12.3 mmol; see step (a) above) in anhydrous THF (50 mL) at -78 °C. After 30 min, triethylborate (2.1 mL, 12.5 mmol) was added and the mixture was allowed to warm to rt and stirred at rt for 2 h. The mixture was poured into water (100 mL), acidified to pH 4 with HCl (aq, 1 M) and extracted with EtOAc (3×50 mL). The combined extracts were washed with brine, dried (Na₂SO₄) and concentrated. The residue was crystallised from petroleum ether to yield 2.07 g (70%) of the sub-title compound.

25 (c) 5-(4-Chloro-3-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 1 from 5-hydroxy-1-(4-isopropoxyphenyl)indol-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-chloro-3-trifluoromethoxyphenylboronic acid (see step 30 (b) above).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.65-7.61 (1H, m) 7.51 (1H, s) 7.35 (1H, s) 7.30-7.25 (2H, m) 7.19 (1H, m) 7.08-6.94 (5H, m) 4.68 (1H, septet, $J = 5.8$ Hz) 1.32 (6H, d, $J = 5.8$ Hz).

5 Example 15

5-(3-Chlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

(a) 5-Benzyloxy-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid ethyl ester

- 10 4-Bromo-2-nitrotoluene (130 mg, 0.6 mmol) in toluene (1.0 mL) and CuI (95.2 mg, 0.5 mmol) and *N,N*-dimethyl-1,2-diaminoethane (106 μL , 1.0 mmol) in toluene (1.0 mL) was added to 5-benzyloxyindole-2-carboxylic acid ethyl ester (150 mg, 0.5 mmol) and K_3PO_4 (220 mg, 1.05 mmol). The mixture was heated at 100-110 $^\circ\text{C}$ for 17 h, cooled and filtered. The solids were washed with acetone
15 and the combined filtrates were concentrated and purified by chromatography to give the sub-title compound (177 mg, 66%).

(b) 5-Hydroxy-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid ethyl ester

- A mixture of 5-benzyloxy-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid
20 ethyl ester (0.58 g, 1.34 mmol; see step (a) above), HCl (aq, conc, 0.23 mL) and EtOAc (30 mL) was hydrogenated at ambient temperature and pressure over 10% Pd-C (0.23 g) for 1.5 h. The mixture was filtered, concentrated and purified by chromatography to give the sub-title compound (0.136 g, 30%).

25 (c) 5-(3-Chlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid ethyl ester

- Anhydrous CH_2Cl_2 (7 mL), Et_3N (160 μL , 1.18 mmol) and pyridine (96 μL , 1.18 mmol) were added to 5-hydroxy-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.59 mmol; see step (b) above), $\text{Cu}(\text{OAc})_2$ (119 mg, 0.59 mmol) and 3-chlorophenylboronic acid (180 mg, 1.18 mmol). The mixture was
30 stirred vigorously at rt for 48 h, filtered through Celite[®], concentrated and purified by chromatography to give the sub-title compound (120 mg, 46%).

(d) 5-(3-Chlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

NaOH (aq, 1 M, 6.0 mL) was added to 5-(3-chlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid ethyl ester (141 mg, 0.30 mmol, see step (c) above) in acetone (3.0 mL). The mixture was stirred at rt for 5 h and acidified with HCl (aq, conc) to pH 2. The mixture was filtered, concentrated and purified by chromatography. Recrystallisation from MeOH/H₂O to afford the title compound (58 mg, 53%).

200-MHz ¹H-NMR (CDCl₃ + DMSO-*d*₆, ppm) δ 8.02-7.97 (1H, m) 7.65-7.53 (2H, m) 7.42-7.37 (2H, m) 7.33-7.21 (1H, m) 7.14 (1H, d, *J* = 9.1 Hz) 7.08-6.98 (2H, m) 6.93-6.83 (2H, m) 2.69 (3H, s).

Example 16

5-(4-Chlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 15 from 5-hydroxy-1-(4-methyl-3-nitrophenyl)indol-2-carboxylic acid ethyl ester (see Example 15 step (b)) and 4-chlorophenylboronic acid.

200 MHz ¹H-NMR (CDCl₃, ppm) δ 8.04-8.00 (1H, m) 7.50 (3H, s) 7.35-7.23 (3H, m, overlapped with CHCl₃) 7.07 (2H, d) 6.96-6.86 (2H, m) 2.73 (3H, s).

Example 17

5-(3,4-Dichlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 15 from 5-hydroxy-1-(4-methyl-3-nitrophenyl)indol-2-carboxylic acid ethyl ester (see Example 15 step (b)) and 3,4-dichlorophenylboronic acid.

200 MHz ¹H-NMR (CDCl₃, ppm) δ 8.02 (1H, t) 7.53-7.49 (3H, m) 7.38-7.32 (2H, m) 7.09-7.05 (2H, m) 7.03 (1H, d, *J* = 2.8 Hz) 6.83 (1H, dd, *J* = 8.9, 2.8 Hz) 2.73 (3H, s).

Example 185-(3-Trifluoromethylphenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 15 from 5-hydroxy-1-(4-methyl-3-nitrophenyl)indol-2-carboxylic acid ethyl ester (see Example 15 step (b)) and 3-trifluoromethylphenylboronic acid.

200 MHz ¹H-NMR (CDCl₃, ppm) δ 8.03 (1H, t) 7.54-7.45 (3H, m) 7.43-7.36 (2H, m) 7.34-7.26 (1H, m) 7.22-7.06 (4H, m) 2.73 (3H, s).

10 Example 195-(3-Trifluoromethoxyphenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 15 from 5-hydroxy-1-(4-methyl-3-nitrophenyl)indol-2-carboxylic acid ethyl ester (see Example 15 step (b)) and 3-trifluoromethoxyphenylboronic acid.

200 MHz ¹H-NMR (CDCl₃, ppm) δ 8.05-8.01 (1H, m) 7.57-7.47 (3H, m) 7.41-7.26 (2H, m) 7.09 (2H, d, *J* = 1.2 Hz) 6.96-6.79 (3H, m) 2.73 (3H, s).

Example 2020 5-(3,5-Dichlorophenoxy)-1-(4-methyl-3-nitrophenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with steps (c) and (d) in Example 15 from 5-hydroxy-1-(4-methyl-3-nitrophenyl)indol-2-carboxylic acid ethyl ester (see Example 15 step (b)) and 3,5-dichlorophenylboronic acid.

200 MHz ¹H-NMR (CDCl₃, ppm) δ 8.05-8.01 (1H, m) 7.58-7.46 (3H, m) 7.40 (1H, dd, *J* = 2.0, 0.8 Hz) 7.01-7.06 (3H, m) 6.83 (2H, d, *J* = 1.9 Hz) 4.6-3.8 (1H, br s) 2.73 (3H, s).

Example 215-(4-Cyclohexylphenoxy)-1-(4-cyclopropoxyphenyl)indole-2-carboxylic acid(a) 1-Bromo-4-(2-bromoethoxy)benzene

- 5 A mixture of 4-bromophenol (30 g, 173 mmol), dibromoethane (40 mL, 464 mmol), NaOH (11.0 g, 275 mmol) and water (430 mL) was heated at reflux for 11 h. The layers were separated and the organic phase was concentrated and distilled to afford the sub-title compound (40.1 g 83 %).

10 (b) 1-Bromo-4-vinyloxybenzene

- KOt-Bu (14.0 g, 125 mmol) was added in portions over 10 min to 1-bromo-4-(2-bromoethoxy)benzene (19.9 g, 100 mmol see step (a) above) in THF (120 mL) at 0 °C. After 16 h at rt, water (400 mL) was added and the mixture was extracted with petroleum ether (4 x 100 mL). The combined extracts were washed with
15 brine, dried (Na₂SO₄), concentrated and distilled under vacuum to yield the sub-title compound (11.5 g, 58%).

(c) 1-Bromo-4-cyclopropoxybenzene

- Diethylzinc (15 % in hexanes, 95.5 mL, 116 mmol) was added to a mixture of
20 1-bromo-4-vinyloxybenzene (11.5 g, 58 mmol), chloro-iodomethane (41 g, 232 mmol) and dichloroethane (180 mL) over 3 h at 0 °C. After 30 min NH₄Cl (aq, sat, 200 mL) and of petroleum ether (300 mL) were added. The organic phase was collected and concentrated. The residue was dissolved in petroleum ether, filtered and concentrated to afford the sub-title compound (11.7 g, 94%).

25

(d) 5-(4-Cyclohexylphenoxy)-1-(4-cyclopropoxyphenyl)indole-2-carboxylic acid

- The title compound was prepared in accordance with steps (a) and (b) in Example 1 from 5-benzyloxyindole-2-carboxylic acid ethyl ester and 1-bromo-4-cyclopropoxybenzene (see step (c) followed by arylation with 4-cyclohexyl-
30 benzenboronic acid in accordance with step (c) in Example 1 and hydrolysis (step (d) in Example 1).

200 MHz ^1H -NMR (CDCl_3 , ppm) δ 12.8-12.7 (1H, br s) 7.34-7.24 (4H, m) 7.21-7.10 (4H, m) 7.02-6.97 (2H, m) 6.89-6.80 (2H, m) 3.69-3.84 (1H, m) 2.47-2.36 (1H, m) 1.83-1.60 (5H, m) 1.46-1.18 (5H, m) 0.88-0.64 (4H, m)

5 Example 22

1-(4-Isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

10 (a) 1-(4-Isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid ethyl ester

A mixture of 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.59 mmol, see Example 1), 2-chloro-5-trifluoromethylpyridine (118 mg, 0.65 mmol) and K_2CO_3 (620 mg, 4.48 mmol) in DMF (8 mL) was heated at 70 °C for 4 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were concentrated and purified by chromatography to afford the sub-title product (220 mg, 77%).

(b) 1-(4-Isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

20 The title compound was prepared in accordance with Example 15 step (d) from 1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid ethyl ester (see step (a) above).

200 MHz ^1H -NMR ($\text{DMSO}-d_6$, ppm) δ 11.3-8.5 (1H, br s) 8.43 (1H, s) 7.88 (1H, dd, $J = 8.5, 1.7$ Hz) 7.51-7.43 (2H, m) 7.24-7.14 (2H, m) 7.13-7.02 (2H, m) 7.02-6.91 (3H, m) 4.62 (1H, septet, $J = 6.2$ Hz) 1.40 (6H, d, $J = 6.2$ Hz).

Example 23

1-(4-Isopropoxyphenyl)-6-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

30 (a) 2-Azido-3-(4-benzyloxyphenyl)acrylic acid ethyl ester

A solution of 4-benzyloxybenzaldehyde (10.00 g, 47.11 mmol) and azidoacetic acid ethyl ester (13.63 g, 118.5 mmol) in EtOH (130 mL) was added dropwise to a

solution of NaOEt (8.06 g, 118.5 mmol) in EtOH (135 mL) at -10° C. The mixture was stirred at -10 °C for 2 h and poured into ice-cooled vigorously stirred NH₄Cl (aq, sat.). The mixture was extracted with EtOAc. The combined extracts were washed with brine, dried (Na₂SO₄), concentrated and purified by chromatography to afford the sub-title compound (10.73 g, 70%).

(b) 6-Benzyloxyindole-2-carboxylic acid ethyl ester

A solution of 2-azido-3-(4-benzyloxyphenyl)-acrylic acid ethyl ester (10.7 g, 33.1 mmol; see step (a) above) in *o*-xylene (150 mL) was added dropwise to boiling *o*-xylene (150 mL). The heating was continued for 10 min and the solution was allowed to cool to rt and kept in a freezer (-18° C) for 16 h. The precipitate was collected, washed with petroleum ether and dried to afford the sub-title compound (7.72 g, 83%).

15 (c) 6-Benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

An oven-dried vial was charged with K₃PO₄ (755 mg, 3.56 mmol), 6-benzyloxyindole-2-carboxylic acid ethyl ester (500 mg, 1.69 mmol, see step (b) above), CuI (32 mg, 0.17 mmol) and flushed with argon. A solution of 4-isopropoxyphenyl bromide (728 mg, 3.38 mmol) in toluene (9.0 mL) was added, followed by *N,N*-dimethyl-1,2-diaminoethane (54 µL, 0.51 mmol). The mixture was heated at 110 °C for 24 h, cooled and filtered through Celite®. The filtrate was concentrated and the residue purified by chromatography to afford the sub-title compound (630 mg, 87%).

25 (d) 6-Hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 6-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (3.12 g, 7.26 mmol; see step (c) above) in EtOAc (50 mL) was hydrogenated at ambient temperature and pressure over 10% Pd-C (1.60 g) for 4 h. The mixture was filtered, concentrated and purified by chromatography to give the sub-title compound (2.35 g, 95%).

(e) 1-(4-Isopropoxy-phenyl)-6-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester

The subtitle compound was prepared in accordance Example 1 step (c) from 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step 5 (d) above) and 4-trifluoromethoxyphenylboronic acid.

(f) 1-(4-Isopropoxyphenyl)-6-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

A mixture of 1-(4-isopropoxyphenyl)-6-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester (156 mg, 0.31 mmol; see step (e) above), NaOH (aq, 1 M, 1.5 mL) and MeCN (10 mL) was heated at reflux for 2 h. The mixture was acidified to pH 2 with HCl (aq, 1 M) and extracted with EtOAc. The combined extracts were concentrated and purified by chromatography to afford the title product (120 mg, 82%).

15 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.73 (1H, s) 7.79 (1H, d, *J* = 8.7 Hz) 7.39 (1H, d, *J* = 0.7 Hz) 7.37-7.30 (2H, m) 7.27-7.18 (2H, m) 7.09-6.94 (4H, m) 6.93 (1H, dd, *J* = 8.7, 2.1 Hz) 6.61-6.56 (1H, m) 4.65 (1H, septet, *J* = 6.0 Hz) 1.30 (6H, d, *J* = 6.0 Hz)

20 Example 24

1-(4-Isopropoxyphenyl)-6-(3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 23 step (d)) and 3-trifluoromethoxyphenylboronic acid in accordance 25 with Example 23 steps (e) and (f).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.7 (1H, br s) 7.81 (1H, d, *J* = 8.8 Hz) 7.45 (1H, dd, *J* = 7.8, 7.8 Hz) 7.39 (1H, d, *J* = 0.8 Hz) 7.27-7.18 (2H, m) 7.12-7.03 (1H, m) 7.02-6.92 (5H, m) 6.63-6.60 (1H, m) 4.65 (1H, septet, *J* = 6.0 Hz) 1.30 (6H, d, *J* = 6.0 Hz).

Example 256-(6-Chloropyridin-2-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid(a) 6-(6-Chloropyridin-2-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.59 mmol, see Example 23 step (d)), 2,6-dichloropyridine (442 mg, 1.5 mmol), K₂CO₃ (1.05 g, 7.60 mmol) and DMF (10 mL) was heated at 90 °C for 26 h. The mixture was poured into water and extracted with EtOAc. The combined extracts were concentrated and purified by chromatography to afford the sub-title product (416 mg, 92%).

(b) 6-(6-Chloropyridin-2-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 23 step (e) from 6-(6-chloropyridin-2-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.75 (1H, s) 7.87 (1H, d, *J* = 7.9 Hz) 7.80 (1H, d, *J* = 8.4 Hz) 7.41 (1H, s) 7.30-7.22 (2H, m) 7.21 (1H, d, *J* = 7.7 Hz) 7.06-6.91 (4H, m) 6.79-6.75 (1H, m) 4.66 (1H, septet, *J* = 6.0 Hz) 1.31 (6H, d, *J* = 6.0 Hz).

Example 261-(4-Isopropoxyphenyl)-6-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 22 step (a) from 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 23 step (d)) and 2-chloro-5-trifluoromethylpyridine (see Example 23 steps (e) and (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.6-12.9 (1H, br s) 8.54-8.48 (1H, m) 8.18 (1H, dd, *J* = 8.8, 2.6 Hz) 7.81 (1H, d, *J* = 8.6 Hz) 7.41 (1H, s) 7.30-7.21 (2H, m) 7.17 (1H, d, *J* = 8.8 Hz) 7.05-6.95 (3H, m) 6.79-6.76 (1H, m) 4.65 (1H, septet, *J* = 6.0 Hz) 1.30 (6H, d, *J* = 6.0 Hz).

Example 276-(3,4-Dichlorophenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from
5 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see
Example 23 step (d)) and 3,4-dichlorophenylboronic acid (see Example 23 steps
(e) and (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.75 (1H, s) 7.80 (1H, d, *J* = 8.7 Hz) 7.56
(1H, d, *J* = 8.9 Hz) 7.41-7.38 (1H, m) 7.30-7.19 (3H, m) 7.04-6.89 (4H, m) 6.66
10 (1H, d, *J* = 1.7 Hz) 4.66 (1H, septet, *J* = 6.0 Hz) 1.30 (6H, d, *J* = 6.0 Hz).

Example 283-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-
carboxylic acid

15

(a) 5-Benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

An oven-dried vial was charged with K₃PO₄ (2.9 g, 13.7 mmol),
5-benzyloxyindole-2-carboxylic acid ethyl ester (2.0 g, 6.77 mmol) and flushed
with argon. A solution of 4-isopropoxyphenylbromide (1.75 g, 8.14 mmol) in
20 toluene (7.0 mL) was added, followed by a solution of CuI (193 mg, 1.01 mmol)
and *N,N'*-dimethyl-1,2-diaminoethane (216 µL, 2.03 mmol) in toluene (5.0 mL).
The mixture was heated at 90 °C for 48 h, cooled, poured into NH₄Cl (aq, sat, 50
mL) and extracted with EtOAc (3 x 50 mL). The combined extracts were washed
with brine, dried (Na₂SO₄), filtered through silica gel and concentrated. The solid
25 residue was recrystallised from EtOAc/petroleum ether to afford 2.5 g (86%) of
the sub-title compound.

(b) 5-Hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A solution of 5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl
30 ester (2.0 g, 4.6 mmol; see step (a) above) in EtOAc (30 mL) and EtOH (30 mL)
was hydrogenated at ambient temperature and pressure over 10% Pd-C (490 mg,
0.546 mmol) for 2 h. The mixture was filtered through silica gel and concentrated.

The residue was crystallised from EtOAc/petroleum ether to give the sub-title compound (1.3 g, 83%).

(c) 5-Acetoxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

- 5 Acetyl chloride (0.85 mL, 11.9 mmol) was added to 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (2.7 g, 7.96 mmol; see step (b) above), DMAP (486 mg, 3.98 mmol) and Et₃N (3.4 mL, 23.9 mmol) in anhydrous CH₂Cl₂ (80 mL). After 12 h at rt, the mixture was poured into water (100 mL). HCl (aq, 1 M, 100 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL).
- 10 The combined extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated to afford 2.9 g (95%) of the sub-title compound.

(d) 5-Acetoxy-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

- 15 SO₂Cl₂ (0.950 mL, 11.8 mmol) was added dropwise over 15 min to 5-acetoxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (4.5 g, 11.8 mmol; see step (c) above) in anhydrous CH₂Cl₂ (200 mL) at 0 °C (dry ice bath). After 2 h at 0 °C, the mixture was poured into NaHCO₃ (aq, sat, 200 mL) and extracted with EtOAc (3 x 100 mL). The combined extracts were washed with water, brine, dried
- 20 (Na₂SO₄), filtered and concentrated to afford 4.0 g (82%) of the sub-title compound.

(e) 3-Chloro-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

- 25 5-Acetoxy-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (1.41 g, 3.39 mmol; see step (d) above) was dissolved in MeOH saturated with ammonia (75 mL). The mixture was kept at 5 °C for 20 h and concentrated. The residue was dissolved in CH₂Cl₂ and filtered through silica gel and concentrated to afford 1.16 g (91%) of the sub-title compound.

(f) 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

Anhydrous CH₂Cl₂ (60 mL), triethylamine (380 µL, 2.68 mmol) and pyridine (220 mL, 2.68 mmol) were added to 3-chloro-5-hydroxy-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (500 mg, 1.34 mmol; see step (e) above), Cu(OAc)₂ (487 mg, 2.68 mmol) and 4-trifluoromethoxyphenyl boronic acid (509 mg, 2.68 mmol). The mixture was stirred vigorously at rt for 24 h, filtered through Celite®, concentrated and purified by chromatography to afford the sub-title compound (465 mg, 67%).

(g) 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

A mixture of 3-chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)-indole-2-carboxylic acid ethyl ester (155 mg, 0.30 mmol; see step (f) above), NaOH (aq, 2 M, 2.0 mL) and dioxane (4 mL) was heated at 120 °C. After cooling to rt the mixture was diluted with brine, neutralized (pH 7) with HCl (aq, 1 M) and extracted with EtOAc. Concentration of the combined extracts and purification by chromatography gave the title product (120 mg, 91%).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.32-7.11 (4H, m) 7.07-6.90 (3H, m) 6.87-6.71 (2H, m) 6.59 (1H, d, *J* = 8.8 Hz) 6.50-6.38 (2H, m) 6.36-6.28 (1H, m) 4.75-4.50 (2H, m) 1.33 (6H, d, *J* = 6.2 Hz) 1.24 (6H, d, *J* = 6.2 Hz).

Example 29

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

(a) 5-(4-*tert*-Butylphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The subtitle compound was prepared in accordance with Example 28 step (f) from 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (b)) and 4-*tert*-butylphenylboronic acid.

(b) 5-(4-*tert*-Butylphenoxy)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A solution of SO₂Cl₂ (243 µL, 3.90 mmol) in anhydrous Et₂O (20 mL) was added over 10 min to 5-(4-*tert*-butylphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (0.943 g, 2.0 mmol, see step (a), above) in anhydrous Et₂O (75 mL) at -9 °C. The mixture was stirred at 0 °C for 24 h, washed with NaHCO₃ (aq, sat), water, and brine, dried (Na₂SO₄) and concentrated. The residue was treated with a small amount of petroleum ether and filtered, affording the sub-

10

(c) 5-(4-*tert*-Butylphenoxy)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28 step (g) from 5-(4-*tert*-butylphenoxy)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (b) above).

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200 MHz ¹H-NMR (CDCl₃, ppm) δ 10.50-8.0 (1H, br s) 7.38-7.28 (3H, m) 7.23-7.14 (2H, m) 7.09 (1H, dd, *J* = 8.9, 2.0 Hz) 7.05-6.85 (5H, m) 4.61 (1H, septet, *J* = 6.0 Hz) 1.39 (6H, d, *J* = 6.0 Hz) 1.31 (9H, s).

20 Example 30

5-(4-*tert*-Butylphenoxy)-3,4-dichloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

(a) 5-(4-*tert*-Butylphenoxy)-3,4-dichloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester.

25

SO₂Cl₂ (80 µL, 0.98 mmol) in anhydrous CH₂Cl₂ (2 mL) was added to 5-(4-*tert*-butylphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.47 mmol; see Example 29, step (a)) in anhydrous CH₂Cl₂ (3 mL) at rt. After 2 h the mixture was poured into NaHCO₃ (aq, sat) (caution! vigorous gas evolution). The phases were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL). The combined extracts were washed with Na₂S₂O₃ (aq,

30

10%), water and brine, dried (Na₂SO₄), concentrated and purified by chromatography to afford the sub-title compound (145 mg, 63 %).

5 (b) 5-(4-*tert*-Butylphenoxy)-3,4-dichloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28 step (g) from 5-(4-*tert*-butylphenoxy)-3,4-dichloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above).

200 MHz ¹H-NMR (CDCl₃, ppm) δ 7.33-7.26 (2H, m) 7.22-7.13 (2H, m) 7.04
10 (1H, d, *J* = 9.1 Hz) 7.00-6.93 (2H, m) 6.90 (1H, d, *J* = 9.1 Hz) 6.86-6.78 (2H, m)
4.61 (1H, septet, *J* = 6.1 Hz) 1.39 (6H, d, *J* = 6.1 Hz) 1.29 (9H, s)

Example 31

15 3-Chloro-1-(4-isopropoxyphenyl)-5-(3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared from 1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid ethyl ester (see Example 22 step (a)) followed by chlorination (see Example 29 step (b) and hydrolysis (see Example 28 step (g)).

20 200 MHz ¹H-NMR (CDCl₃, ppm) δ 7.43-7.39 (1H, m) 7.36-7.27 (1H, m) 7.25-7.17 (2H, m) 7.11-7.07 (2H, m) 7.02-6.81 (5H, m) 4.61 (1H, septet, *J* = 6.0 Hz) 1.40 (6H, d, *J* = 6.1 Hz).

Example 32

25 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared from 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (b)) and 4-trifluoromethoxyphenylboronic acid (see Example 28 step (f)) followed by chlorination
30 (see Example 29 step (b)) and hydrolysis (see Example 28 step (g)).

200 MHz ^1H -NMR (CDCl_3 , ppm) δ 7.37-7.33 (1H, m) 7.24-7.12 (4H, m) 7.08-7.04 (2H, m) 7.02-6.89 (4H, m) 4.59 (1H, septet, $J = 6.1$ Hz) 1.38 (6H, d, $J = 6.1$ Hz).

5 Example 33

3-Chloro-5-(4-chloro-3-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28 step (f) from 3-chloro-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (e)) and 4-chloro-3-trifluoromethoxyphenylboronic acid (see Example 14, step (b)) followed by hydrolysis (see Example 28 step (g)). 200 MHz ^1H -NMR ($\text{DMSO}-d_6$, ppm) δ 3.3 (1H, br s) 7.66 (1H, d, $J = 8.9$ Hz) 7.40 (1H, dd, $J = 2.0, 0.7$ Hz) 7.35-7.27 (2H, m) 7.27-7.23 (1H, m) 7.19 (1H, dd, $J = 9.0, 2.0$ Hz) 7.12 (1H, dd, $J = 9.0, 0.7$ Hz) 7.09-7.00 (2H, m) 7.01 (1H, dd, $J = 8.9, 2.8$ Hz) 4.69 (1H, septet, $J = 6.0$ Hz) 1.32 (6H, d, $J = 6.0$ Hz).

Example 34

3-Chloro-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)-indole-2-carboxylic acid

20

(a) 4-Bromo-2-trifluoromethoxyphenol

Bromine (1.0 M in CH_2Cl_2 , 45 mmol, 45 mL) was added dropwise to 2-trifluoromethoxyphenol (7.40 g, 41.5 mmol) in CH_2Cl_2 (100 mL) at -78°C . The mixture was allowed to warm to rt and was stirred for 48 hours. Na_2SO_3 (aq, sat, 100 mL) was added, and the mixture was stirred vigorously until the orange color disappeared. The mixture was diluted with CH_2Cl_2 (200 mL) and the organic layer collected, washed with brine, dried (Na_2SO_4) and concentrated to afford 9.6 g (91%) of the sub-title product.

30 (b) 4-Bromo-1-isopropoxy-2-trifluoromethoxybenzene

A mixture of 4-bromo-2-trifluoromethoxyphenol (9.6 g, 37.4 mmol), 2-bromopropane (7.0 mL, 74.7 mmol) and NaOH (3.0 g, 74.7 mmol) in anhydrous DMF

(25 mL) was heated at 70 °C for 2 h, poured into water (100 mL) and extracted with *t*-BuOMe (3 x 100 mL). The combined extracts were washed with brine, dried (Na₂SO₄), concentrated and distilled (bulb-to-bulb, 150 °C, 9.8 x 10⁻² Torr) to yield 9.5 g (85%) of the sub-title compound.

5

(c) 4-Isopropoxy-3-trifluoromethoxyphenylboronic acid

The sub-title compound was prepared in accordance with Example 14 step (b) from 4-bromo-1-isopropoxy-2-trifluoromethoxybenzene (see step (b) above).

10 (d) 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28 step (f) from 3-chloro-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (e)) and 4-isopropoxy-3-trifluoromethoxyphenylboronic acid (see step (c) above) followed by hydrolysis (see Example 28 step (g)).

15

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.3 (1H, br s) 7.34-7.19 (4H, m) 7.17-7.04 (4H, m) 7.03-6.95 (2H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 4.62 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz) 1.27 (6H, d, *J* = 6.0 Hz).

20 Example 35

3-Chloro-5-(2,2-difluorobenzo[1,3]dioxol-5-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

(a) 2,2-Difluorobenzo[1,3]dioxole-5-boronic acid

25 The sub-title compound was prepared in accordance with Example 14 step (b) from 5-bromo-2,2-difluorobenzo[1,3]-dioxole.

(b) 3-Chloro-5-(2,2-difluorobenzo[1,3]dioxol-5-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

30 The title compound was prepared in accordance with Example 28 step (f) from 3-chloro-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

(see Example 28 step (e)) and 2,2-difluorobenzo[1,3]dioxole-5-boronic acid (see step (a) above) followed by hydrolysis (see Example 28 step (g)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.5-13.2 (1H, br s) 7.39 (1H, d, $J = 8.4$ Hz) 7.34-7.23 (4H, m) 7.14 (1H, dd, $J = 9.0, 2.2$ Hz) 7.11-7.09 (1H, m) 7.08-6.99 (2H, m) 6.82 (1H, dd, $J = 8.8, 2.4$ Hz) 4.69 (1H, septet, $J = 6.0$ Hz) 1.32 (6H, d, $J = 6.0$ Hz).

Example 36

3-Chloro-5-(3-fluoro-4-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

(a) 3-Fluoro-4-trifluoromethoxyphenylboronic acid

The sub-title compound was prepared in accordance with Example 14 step (b) from 4-bromo-2-fluoro-1-trifluoromethoxybenzene.

(b) 3-Chloro-5-(3-fluoro-4-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28 step (f) from 3-chloro-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (e)) and 3-fluoro-4-trifluoromethoxyphenylboronic acid (see step (a) above) followed by hydrolysis (see Example 28 step (g)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.39 (1H, s) 7.61-7.49 (1H, m) 7.41 (1H, dd, $J = 1.6, 0.6$ Hz) 7.36-7.26 (2H, m) 7.19 (1H, dd, $J = 9.0, 2.2$ Hz) 7.06-6.99 (4H, m) 6.89-6.81 (1H, m) 4.69 (1H, septet, $J = 6.0$ Hz) 1.32 (6H, d, $J = 6.0$ Hz).

Example 37

1-(4-Acetylaminophenyl)-3-chloro-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

- 5 (a) 1-(4-Acetylaminophenyl)-5-benzyloxy-3-chloroindole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 28, step (a) from 5-benzyloxyindole-2-carboxylic acid ethyl ester and (4-acetylamino)-phenylboronic acid, followed by chlorination (see Example 29, step (b)).

10

- (b) 1-(4-Acetylaminophenyl)-3-chloro-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 23, step (d) from 1-(4-acetylaminophenyl)-5-benzyloxy-3-chloroindole-2-carboxylic acid ethyl ester, followed by *O*-arylation (see Example 1, step (c)).

15

- (c) 1-(4-Acetylaminophenyl)-3-chloro-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 28, step (g) from 1-(4-acetylaminophenyl)-3-chloro-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (see step (b) above).

20

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 10.14 (1H, s) 7.80-7.63 (4H, m) 7.40-6.96 (7H, m) 2.08 (3H, s)

25 Example 38

3-Chloro-1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

The title compound was prepared from 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 28 step (b)) and 2-chloro-5-trifluoromethylpyridine (see Example 22 step (a)) followed by chlorination (see Example 29 step (b)) and hydrolysis (see Example 28 step (g)).

30

200 MHz ^1H -NMR (CDCl_3 , ppm) δ 10.7-8.7 (1H, br s) 8.42 (1H, m) 7.90 (1H, dd, $J = 8.7, 2.3$ Hz) 7.55-7.50 (1H, m) 7.23-7.14 (2H, m) 7.13-7.08 (2H, m) 7.05 (1H, d, $J = 8.7$ Hz) 7.01-6.90 (2H, m) 4.61 (1H, septet, $J = 6.1$ Hz) 1.40 (6H, d, $J = 6.0$ Hz).

5

Example 39

3-Chloro-1-(4-cyclopentyloxyphenyl)-5-(4-trifluoromethoxybenzoyl)indole-2-carboxylic acid

10 (a) 5-Bromo-3-chloroindole-2-carboxylic acid ethyl ester

A mixture of 5-bromo-3-chloroindole-2-carboxylic acid ethyl ester (10.0 g, 37.3 mmol), SO_2Cl_2 (4.5 mL, 55.5 mmol) and benzene (250 mL) was heated at reflux for 2 h. Concentration to ca. 120 mL, cooling to rt and filtration afforded the sub-title compound (6.33 g, 56% yield).

15

(b) 5-Bromo-3-chloro-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid ethyl ester

Anhydrous CH_2Cl_2 (80 mL), Et_3N (2.7 mL, 19.8 mmol), pyridine (1.6 mL, 19.8 mmol) and 3 Å molecular sieves (ca. 3 g) were added to 5-bromo-3-chloroindole-2-carboxylic acid ethyl ester (3 g, 9.9 mmol; see step (a) above), $\text{Cu}(\text{OAc})_2$ (3.6 g, 19.8 mmol), and 4-cyclopentyloxyphenylboronic acid (4.08 g, 19.8 mmol). The mixture was stirred vigorously at rt for 30 h and filtered through Celite®. The solids were washed with EtOAc and the combined filtrates were concentrated and purified by chromatography to afford the sub-title compound (3.4 g, 75%).

25

(c) 3-Chloro-1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester

A mixture of 5-bromo-3-chloro-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid ethyl ester (3.72 g, 8.04 mmol; see step (b)), CuI (0.152 g, 0.8 mmol), N,N' -dimethyl-1,2-diaminoethane (170 μL , 1.6 mmol), NaI (2.41 g, 16.0 mmol) and dioxane (15 mL) was heated at 110 °C for 72 h, cooled to rt, diluted with NH_4Cl (aq, sat), poured into water (200 mL) and extracted with EtOAc. The combined

30

extracts were washed with water, brine, dried (Na_2SO_4), filtered through silica gel and concentrated to afford the sub-title compound (3.68g, 72%).

5 (d) 3-Chloro-1-(4-cyclopentyloxyphenyl)-5-(4-trifluoromethoxybenzoyl)indole-2-carboxylic acid ethyl ester

A solution of 3-chloro-1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester (255 mg, 0.5 mmol) was added dropwise to *i*-PrMgCl·LiCl in THF (1 M in THF, 0.5 mL, 0.5 mmol) at -40 °C under argon. After 15 min., 4-trifluoromethoxybenzoyl chloride (0.24 mL, 1.5 mmol) was added and the mixture was
10 allowed to warm to rt. NH_4Cl (aq, sat, 2.0 mL) was added and the mixture was extracted with EtOAc. The combined extracts were washed with water, brine and dried (Na_2SO_4). Concentration and purification by chromatography afforded the sub-title compound (210 mg, 73%).

15 (e) 3-Chloro-1-(4-cyclopentyloxyphenyl)-5-(4-trifluoromethoxybenzoyl)indole-2-carboxylic acid

A mixture of 3-chloro-1-(4-cyclopentyloxyphenyl)-5-(4-trifluoromethoxybenzoyl)indole-2-carboxylic acid ethyl ester (165 mg, 0.29 mmol; see step (d)), dioxane (2 mL) and NaOH (aq, 2 M, 1.0 mL, 2.0 mmol) was heated by microwave
20 irradiation at 120 °C for 15 min. After cooling, a few drops of water were added, and the pH was adjusted to ca 2 by addition of HCl (aq, 2 M). The white precipitate was filtered off and recrystallised from EtOAc/petroleum ether to yield 156 mg (99%) of the title compound.

200 MHz ^1H -NMR ($\text{DMSO}-d_6$, ppm) δ 8.03-8.02 (1H, m) 7.92-7.85 (2H, m) 7.79
25 (1H, dd, $J = 8.8, 1.7$ Hz) 7.57-7.53 (2H, m) 7.63-7.29 (2H, m) 7.19 (1H, d, $J = 9.0$ Hz) 7.07-6.99 (2H, m) 4.92-4.83 (1H, m) 2.01-1.54 (8H, m).

Example 40

30 3-Chloro-5-(4-chlorobenzoyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 39, step (d) from 3-chloro-1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester

(see Example 39, step (c)) and 4-chlorobenzoyl chloride, followed by hydrolysis (see Example 39, step (e)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.6-13.4 (1H, br s) 8.02-8.01 (1H, m) 7.80-7.74 (3H, m) 7.67-7.61 (2H, m) 7.36-7.29 (2H, m) 7.19 (1H, d, $J = 8.8$ Hz) 5 7.07-7.00 (2H, m) 4.92-4.83 (1H, m) 2.02-1.54 (8H, m).

Example 41

3-Chloro-1-(4-cyclopentyloxyphenyl)-5-(3-isopropoxybenzoyl)indole-2-carboxylic acid

10 The title compound was prepared in accordance with Example 39, step (d) from 3-chloro-1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester (see Example 39, step (c)) and 3-isopropoxybenzoyl chloride, followed by hydrolysis (see Example 39, step (e)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.6-13.4 (1H, br s) 8.03-8.02 (1H, m) 15 7.79 (1H, dd, $J = 8.8, 1.6$ Hz) 7.50-7.41 (1H, m) 7.36-7.29 (2H, m) 7.27-7.16 (4H, m) 7.07-7.00 (2H, m) 4.91-4.84 (1H, m) 4.66 (1H, septet, $J = 6.0$ Hz) 2.03-1.55 (8H, m) 1.27 (6H, d, $J = 6.0$ Hz)

Example 42

3-Chloro-5-(6-chloropyridine-3-carbonyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 39, step (d) from 3-chloro-1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester (see Example 39, step (c)) and 6-chloronicotinoyl chloride, followed by hydrolysis (see Example 39, step (e)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 14.0-13.0 (1H, br s) 8.73 (1H, dd, $J = 2.4, 0.8$ Hz) 8.18 (1H, dd, $J = 8.3, 2.4$ Hz) 8.07 (1H, dd, $J = 1.6, 0.6$ Hz) 7.82 (1H, dd, $J = 8.8, 1.6$ Hz) 7.73 (1H, dd, $J = 8.3, 0.8$ Hz) 7.37-7.29 (2H, m) 7.20 (1H, dd, $J = 8.8, 0.6$ Hz) 7.07-6.99 (2H, m) 4.92-4.84 (1H, m) 2.02-1.56 (8H, m).

Example 433-Chloro-1-(4-isopropoxyphenyl)-5-(3-trifluoromethylbenzyl)indole-2-carboxylic acid5 (a) 3-Chloro-5-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 39 step (b) from 5-bromo-3-chloroindole-2-carboxylic acid ethyl ester (see step (a) Example 39) and 4-isopropoxyphenylboronic acid followed by bromine-iodine exchange (see Example 39 step (c)).

10

(b) 3-Chloro-5-(dihydroxyboryl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

i-PrMgCl·LiCl (0.95 M in THF, 3.26 mL, 3.1 mmol) was added over 5 min to 3-chloro-5-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (1.45 g, 3.0 mmol, see step (a) above) in THF (9 mL) at -40 °C. After 15 min at -40 °C, B(OEt)₃ (1.56 mL, 9.0 mmol) was added. The temperature was allowed to reach 0 °C over 2 h and HCl (aq, 2.5 M, 14.4 mL, 36 mmol) was added. After 1 h at 0 °C, the mixture was diluted with brine (70 mL) and extracted with *t*-BuOMe (4x70 mL). The combined extracts were washed with brine (100 mL), dried (Na₂SO₄) and concentrated. The solid residue was treated several times with petroleum ether and filtered to give the sub-title compound (1.04 g, 86 %)

20

(c) 3-Chloro-1-(4-isopropoxyphenyl)-5-(3-trifluoromethylbenzyl)indole-2-carboxylic acid ethyl ester

25 A mixture of 3-chloro-5-(dihydroxyboryl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (160 mg, 0.4 mmol; see step (b)), 3-trifluoromethylbenzylbromide (0.25 mL, 1.6 mmol) Pd(OA)₂ (4.5 mg, 0.02 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), K₃PO₄ (2.41 g, 16.0 mmol) and toluene (2 mL) was heated at 120 °C for 24 h, cooled to rt, diluted with EtOAc, washed with water and brine, dried (Na₂SO₄), concentrated and purified by chromatography to afford the sub-title compound (109 mg, 53%).

30

(d) 3-Chloro-1-(4-isopropoxyphenyl)-5-(3-trifluoromethylbenzyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-1-(4-isopropoxyphenyl)-5-(3-trifluoromethylbenzyl)indole-2-carboxylic acid ethyl ester (see step (c) above)

5 followed by hydrolysis (see Example 28 step (g)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.4-13.1 (1H, br s) 7.65-7.43 (5H, m) 7.28-7.16 (3H, m) 7.06-6.92 (3H, m) 4.64 (1H, septet, *J* = 6.0 Hz) 4.05 (2H, s) 1.28 (6H, d, *J* = 6.0 Hz)

10 Example 44

3-Chloro-5-(3-chlorobenzyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-5-(dihydroxyboryl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 43 step (b)) and 3-chlorobenzylchloride (see Example 43 step (c)) followed by hydrolysis

15 (see Example 28 step (g)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.54 (1H, s) 7.76-7.14 (7H, m) 7.04-6.96 (3H, m) 4.64 (1H, septet, *J* = 6.0 Hz) 4.12 (2H, s) 1.28 (6H, d, *J* = 6.0 Hz).

Example 45

20 5-(3-Chlorophenylsulfanyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid

(a) 1-(4-Cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 39 step (b) from 5-bromoindole-2-carboxylic acid ethyl ester and 4-cyclopentyloxyphenylboronic acid followed by bromine-iodine exchange (see Example 39 step (c)).

(b) 5-(3-Chlorophenylsulfanyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid ethyl ester

30 A mixture of 1-(4-cyclopentyloxyphenyl)-5-iodoindole-2-carboxylic acid ethyl ester (180 mg, 0.38 mmol; see step (a)), 3-chlorobenzenethiol (46 μL, 0.42 mmol) Pd₂(dba)₃ (10.4 mg, 0.011 mmol), DPEphos (12.2 mg, 0.023 mmol), KO^t-Bu

(47.1 g, 0.42 mmol) and toluene (3 mL) was heated at 100 °C for 2 h. The mixture was cooled to rt, diluted with EtOAc, filtered through Celite[®], concentrated and purified by chromatography to afford the sub-title compound (140 mg, 75%).

5 (c) 5-(3-Chlorophenylsulfanyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid

The title compound was prepared from 5-(3-chlorophenylsulfanyl)-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid ethyl ester (see step (b) above) followed by hydrolysis (see Example 23 step (f)).

10 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.12.9-12.8 (1H, br s) 7.99 (1H, d, *J* = 1.8 Hz) 7.42-7.16 (6H, m) 7.13-6.96 (5H, m) 4.93-4.80 (1H, m) 2.01-1.51 (8H, m).

Example 46

15 3-Chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

(a) 3-Chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester.

20 The sub-title compound was prepared from 3-chloro-5-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 43 step (a)) and 4-chlorobenzenethiol (see Example 45 step (b)).

25 (b) 3-Chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above) followed by hydrolysis (see Example 23 step (f)).

30 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.6-13.4 (1H, br s) 7.80 (1H, d, *J* = 1.4 Hz) 7.45-7.25 (5H, m) 7.24-7.15 (2H, m) 7.12 (1H, d, *J* = 8.8 Hz) 7.08-7.00 (2H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz).

Example 473-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid5 (a) 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid ester

The sub-title compound was prepared from 3-chloro-5-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 43 step (a)) and 4-trifluoromethylbenzenethiol (see Example 45 step (b)).

10

(b) 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid ester (see step (a) above)

15 followed by hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.8-13.2 (1H, br s) 7.88 (1H, d, *J* = 1.5 Hz) 7.66-7.53 (2H, m) 7.43 (1H, dd, *J* = 8.8, 1.5 Hz) 7.35-7.20 (4H, m) 7.20-7.11 (1H, m) 7.07-6.96 (2H, m) 4.67 (1H, septet, *J* = 5.9 Hz) 1.30 (6H, d, *J* = 5.9 Hz).

20 Example 483-Chloro-5-(4-chlorobenzenesulfinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid25 (a) 3-Chloro-5-(4-chlorobenzenesulfinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 3-chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (150 mg, 0.3 mmol; see step (a) Example 46), Bu₄NIO₄ (143 mg, 0.33 mmol), 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine iron (III) chloride (4 mg, 0.006 mmol) and CH₂Cl₂ (2 mL) was stirred at rt for 3.5 h, diluted with CH₂Cl₂, filtered through silica gel, concentrated and purified by chromatography to afford the sub-title compound (87 mg, 56%).

30

(b) 3-Chloro-5-(4-chlorobenzenesulfinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-5-(4-chlorobenzenesulfinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above)

5 followed by hydrolysis (see Example 1, step (d)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.6 (1H, br s) 8.15 (1H, d, *J* = 1.5 Hz) 7.81-7.70 (2H, m) 7.65-7.56 (2H, m) 7.54 (1H, dd, *J* = 9.0 1.5 Hz) 7.33-7.23 (2H, m) 7.17 (1H, d, *J* = 9.0 Hz) 7.07-6.96 (2H, m) 4.67 (1H, septet, *J* = 6.0 Hz) 1.31 (6H, d, *J* = 6.0 Hz).

10

Example 49

3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylbenzenesulfinyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid ester (see step (a) Example 47) by oxidation (see Example 48, step (a)) followed by hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 8.00-7.82 (4H, m) 7.61-7.50 (1H, m) 7.31-7.20 (2H, m) 7.20-7.11 (1H, m) 7.04-6.93 (2H, m) 4.65 (1H, septet, *J* = 6.2 Hz) 1.28 (6H, d, *J* = 6.2 Hz).

20

Example 50

3-Chloro-5-(4-chlorobenzenesulfonyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

25

(a) 3-Chloro-5-(4-chlorobenzenesulfonyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 3-chloro-5-(4-chlorophenylsulfanyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (200 mg, 0.4 mmol; see step (a) Example 46),

30 Oxone[®] (1.23 g, 2.0 mmol), THF (3 mL) and water (4 mL) was stirred at rt for 3 d, diluted with water and extracted with EtOAc. The combined extracts were

washed with water and brine, concentrated and purified by chromatography to afford the sub-title compound (165 mg, 77%).

5 (b) 3-Chloro-5-(4-chlorobenzenesulfonyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-5-(4-chlorobenzenesulfonyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above) followed by ester hydrolysis (see Example 23, step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.7-12.6 (1H, br s) 8.32-8.23 (1H, m)
10 8.03-7.93 (2H, m) 7.84-7.73 (1H, m) 7.71-7.60 (2H, m) 7.35-7.24 (2H, m) 7.20
(1H, d, *J* = 8.8 Hz) 7.07-6.95 (2H, m) 4.66 (1H, septet, *J* = 5.9 Hz) 1.29 (6H, d, *J*
= 5.9 Hz).

Example 51

15 3-Chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylbenzenesulfonyl)indole-2-carboxylic acid

The title compound was prepared from 3-chloro-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenylsulfanyl)indole-2-carboxylic acid ester (see step (a) Example 47) by oxidation (see Example 50, step (a)) followed by hydrolysis (see
20 Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 3.8-13.15 (1H, br s) 8.35 (1H, d, *J* = 1.5
Hz) 8.26-8.15 (2H, m) 8.01-7.91 (2H, m) 7.84 (1H, dd, *J* = 8.8, 1.5 Hz) 7.34-7.26
(2H, m) 7.26-7.19 (1H, m) 7.07-6.96 (2H, m) 4.66 (1H, septet, *J* = 5.9 Hz) 1.26
(6H, d, *J* = 5.9 Hz)

Example 521-(4-Isopropoxyphenyl)-3-methanesulfonylamino-5-(4-trifluoromethylphenoxy)-indole-2-carboxylic acid5 (a) 3-Bromo-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

A mixture of 1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (452 mg, 0.93 mmol, see Example 9), NBS (360 mg, 2.00 mmol) and CCl₄ (10 mL) was heated at 80 °C for 14 h. The mixture was
10 poured into Na₂S₂O₃ (aq, 10%) and extracted with CH₂Cl₂. The combined extracts were washed with water, dried (Na₂SO₄) and purified by chromatography to give 489 mg (93%) of the sub-title compound.

15 (b) 1-(4-Isopropoxyphenyl)-3-methanesulfonylamino-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

An oven-dried pressure tube was charged with 3-bromo-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (300 mg, 0.53 mmol, see step (a) above), methanesulfonamide (101 mg, 1.06 mmol), Cs₂CO₃ (209 mg, 0.80 mmol), Pd₂(dba)₃ and xantphos (47 mg, 0.08 mmol). The tube was
20 flushed with argon and dioxane (5 mL) was added. The mixture was heated at 90 °C for 48 h, cooled and filtered through Celite®. The filtrate was concentrated and purified by chromatography affording the sub-title compound (260 mg, 85%).

25 (c) 1-(4-Isopropoxyphenyl)-3-methanesulfonylamino-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 23 step (f) from 1-(4-isopropoxyphenyl)-3-methanesulfonylamino-5-(4-trifluoromethylphenoxy)-indole-2-carboxylic acid ethyl ester (see step (b), above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.0-11.0 (1H, br s) 7.72-7.63 (2H, m)
30 7.61-7.57 (1H, m) 7.25-7.15 (2H, m) 7.12-7.03 (2H, m) 7.03-6.90 (4H, m) 4.66 (1H, septet, *J* = 6.0 Hz) 2.85 (3H, s) 1.32 (6H, d, *J* = 6.0 Hz).

Example 53

1-(4-Isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

- 5 (a) 1-(4-Isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

An oven-dried pressure tube was charged with 3-bromo-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (170 mg, 0.30 mmol, see Example 52 step (a)), nicotinamide (74 mg, 0.60 mmol), K₃PO₄ (135 mg, 0.64 mmol) and CuI (12 mg, 0.06 mmol). The tube was flushed with argon and dioxane (4 mL) followed by *N,N*-dimethyl-1,2-diaminoethane (16 µL, 0.15 mmol) were added. The mixture was heated at 90 °C for 24 h, cooled, filtered through Celite[®], concentrated and purified by chromatography to give the sub-title compound (82 mg, 45%).

15

- (b) 1-(4-Isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 23 step (f) from 1-(4-isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (see step (a), above).

20

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.5-12.5 (1H, br s) 10.60 (1H, s) 9.18-9.12 (1H, m) 8.76 (1H, dd, *J* = 4.6, 1.2 Hz) 8.36-8.28 (1H, m) 7.72-7.64 (2H, m) 7.61-7.52 (2H, m) 7.33-7.25 (2H, m) 7.13-7.01 (6H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 1.31 (6H, d, *J* = 6.0 Hz).

25

Example 54

1-(4-Isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 53 step (a) from 3-bromo-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (see Example 52 step (a)) and pyrrolidin-2-one, followed by hydrolysis (see Example 23 step (f)).

30

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.3-13.0 (1H, br s) 7.71-7.67 (2H, m) 7.34-7.25 (3H, m) 7.12 (1H, d, *J* = 9.0 Hz) 7.09-6.96 (5H, m) 4.65 (1H, septet, *J* = 6.0 Hz) 3.81 (2H, t, *J* = 6.0 Hz) 2.39 (2H, t, *J* = 8.0 Hz) 2.18-2.01 (2H, m) 1.30 (6H, d, *J* = 6.0 Hz).

5

Example 55

3-(4-Dimethylaminobutyrylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 52 step (b) from
10 3-bromo-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (see Example 52 step (a)) and 4-dimethylaminobutyramide followed by hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.85-7.81 (1H, m) 7.73-7.64 (2H, m) 7.22-7.13 (2H, m) 7.10-7.01 (2H, m) 7.01-6.94 (4H, m) 4.65 (1H, septet, *J* = 6.0 Hz)
15 2.92-2.81 (2H, m) 2.56 (6H, s) 2.53-2.39 (2H, m, overlapped with DMSO) 1.99-1.81 (2H, m) 1.31 (6H, d, *J* = 6.0 Hz).

Example 56

3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

20

(a) 3-Bromo-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1 step (c) from
25 5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 1 step (b)) and 4-isopropoxy-3-trifluoromethoxyphenyl boronic acid (Example 34 step (a-c)) followed by bromination (see Example 52 step (a)).

(b) 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

30

The sub-title compound was prepared in accordance with Example 52 step (b) from 3-bromo-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphen-

oxy)indole-2-carboxylic acid ethyl ester (see step (a) above) and 2,2-dimethylpropionamide followed by hydrolysis (see Example 23 step (f)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.6-12.7 (1H, br s) 10.5-10.0 (1H, br s) 7.57 (1H, s) 7.26-7.16 (3H, m) 7.06-6.94 (5H, m) 6.89 (1H, dd, $J = 9.0, 2.8$ Hz) 4.67 (1H, septet, $J = 6.0$ Hz) 4.59 (1H, septet, $J = 6.0$ Hz) 1.32 (6H, d, $J = 6.0$ Hz) 1.25 (6H, d, $J = 6.0$ Hz) 1.24 (9H, s).

Example 57

10 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

(a) 5-Benzyloxy-3-iodoindole-2-carboxylic acid ethyl ester

A solution of NaI (3.05 g, 20.33 mmol) in acetone (70 mL) was added dropwise to *N*-chlorosuccinimide (2.71 g, 20.33 mmol) in acetone (50 mL) protected from
15 light. After 15 min, a solution of 5-benzyloxyindole-2-carboxylic acid ethyl ester (5.00 g, 16.93 mmol) in acetone (145 mL) was added dropwise, followed by stirring for 30 min at rt. The mixture was poured into $\text{Na}_2\text{S}_2\text{O}_3$ (aq, 10%, 250 mL) and extracted with EtOAc. The combined extracts were washed with NaHCO_3 (aq, sat), water and brine, dried (Na_2SO_4) and concentrated. The residue was
20 crystallised from EtOH to give the sub-title compound (7.13 g, 87%).

(b) 5-Benzyloxy-3-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

Anhydrous CH_2Cl_2 (100 mL), Et_3N (3.34 mL, 23.74 mmol) and pyridine (1.94
25 mL, 23.74 mmol) were added to 5-benzyloxy-3-iodoindole-2-carboxylic acid ethyl ester (5.00 g, 11.87 mmol; see step (a) above), $\text{Cu}(\text{OAc})_2$ (4.31 g, 23.74 mmol), 3 Å molecular sieves (ca. 8 g) and 4-isopropoxyphenylboronic acid (4.27 g, 23.74 mmol). The mixture was stirred vigorously at rt for 24 h and filtered through Celite®. The solids were washed with EtOAc and the combined filtrates
30 concentrated and purified by chromatography to afford the sub-title compound (6.07 g, 92%).

(c) 5-Benzoyloxy-3-(2,2-dimethylpropionylamino)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The subtitle product was prepared in accordance with Example 53 step (a) from 5-benzoyloxy-3-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester
5 (see step (b) above) and 2,2-dimethylpropionamide.

(d) 3-(2,2-Dimethylpropionylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The subtitle product was prepared in accordance with Example 23 step (d) from
10 5-benzoyloxy-3-(2,2-dimethylpropionylamino)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (c) above).

(e) 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

15 The title compound was prepared in accordance with Example 1 step (c) from 3-(2,2-dimethylpropionylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (d) above) and 4-trifluoromethoxyphenylboronic acid (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.5-12.5 (1H, br s) 9.76 (0.8H, s) 8.88 (0.2 H, s) 7.65-7.44 (3H, m) 7.32-7.16 (2H, m) 7.16-6.95 (5H, m) 7.71-6.89 (1H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 1.43 (1.8H, s) 1.32 (6H, d, *J* = 6.0 Hz) 1.26 (7.2H, s).

Example 58

25 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from 3-(2,2-dimethylpropionylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 57 step (d)) and 4-trifluoromethylphenylboronic acid according to Example 23 step (f).
30

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.4-13.0 (1H, br s) 10.3-10.0 (1H, br s) 7.74-7.62 (3H, m) 7.29-7.17 (2H, m) 7.10-6.95 (6H, m) 4.67 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz) 1.25 (9H, s).

5 Example 59

5-(4-Chloro-3-trifluoromethoxyphenoxy)-3-(2,2-dimethylpropionylamino)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from 3-(2,2-dimethylpropionylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 57 step (d)) and 4-chloro-3-trifluoromethoxyphenylboronic acid (see Example 14, step (b)), followed by hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 9.64 (1H, s) 7.64 (1H, d, *J* = 8.0 Hz) 7.57 (1H, d, *J* = 1.8 Hz) 7.30-7.21 (2H, m) 7.21-7.12 (1H, m) 7.11-7.00 (4H, m) 6.93 (1H, dd, *J* = 9.1, 2.9 Hz) 4.68 (1H, septet, *J* = 6.0 Hz) 1.32 (6H, d, *J* = 6.0 Hz) 1.26 (9H, s).

Example 60

3-[(2,2-Dimethylpropionyl)methylamino]-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

(a) 5-Benzyloxy-3-[(2,2-dimethylpropionyl)methylamino]-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

5-Benzyloxy-3-(2,2-dimethylpropionylamino)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (1.00 g, 1.89 mmol; see Example 57 step (c)) in DMF (20 mL) was added to a stirred suspension of NaH (67 mg, 2.08 mmol; 75% suspension in mineral oil) in DMF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 25 min. A solution of MeI (235 μL, 3.78 mmol) in DMF (10 mL) was added in portions and the mixture was stirred at rt for 24 h, poured into water and extracted with *t*-BuOMe. The combined extracts were washed with water and brine, dried (Na₂SO₄), concentrated and purified by chromatography to give the sub-title compound (500 mg, 49%).

(b) 3-[(2,2-Dimethylpropionyl)methylamino]-5-hydroxy-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester

The sub-title product was prepared in accordance to Example 23 step (d) from
 5 5-benzyloxy-3-[(2,2-dimethylpropionyl)methylamino]-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (see step (a) above).

(c) 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

10 The title compound was prepared in accordance with Example 1 step (c) from 3-[(2,2-dimethylpropionyl)methylamino]-5-hydroxy-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (see step (b) above) and 4-trifluoromethylphenylboronic acid, followed by hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.72-7.62 (2H, m) 7.32-7.19 (3H, m) 7.16-
 15 6.96 (6H, m) 4.65 (1H, septet, *J* = 6.0 Hz) 3.12 (3H, s) 1.30 (6H, d, *J* = 6.0 Hz) 0.95 (9H, s).

Example 61

5-(4-Chloro-3-trifluoromethoxyphenoxy)-3-[(2,2-dimethylpropionyl)methylamino]-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

20 The title compound was prepared in accordance with Example 1 step (c) from 3-[(2,2-dimethylpropionyl)methylamino]-5-hydroxy-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (see Example 60 step (b)) and 4-chloro-3-trifluoromethoxyphenyl boronic acid (see Example 14, step (b)) followed by
 25 hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.4-13.1 (1H, br s) 7.66 (1H, d, *J* = 8.8 Hz) 7.38-7.33 (1H, m) 7.31-7.23 (2H, m) 7.18-7.12 (3H, m) 7.09-7.01 (2H, m) 7.01 (1H, dd, *J* = 8.8, 2.8 Hz) 4.69 (1H, septet, *J* = 6.0 Hz) 3.13 (3H, s) 1.32 (6H, d, *J* = 6.0 Hz) 0.96 (9H, s).

Example 62

3-[(2,2-Dimethylpropionyl)methylamino]-5-(3-fluoro-4-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from
5 3-[(2,2-dimethylpropionyl)methylamino]-5-hydroxy-1-(4-isopropoxyphenyl)-
indole-2-carboxylic acid ethyl ester (see Example 60 step (b)) and 3-fluoro-4-
trifluoromethoxyphenylboronic acid (see Example 36, step (a)) followed by
hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.4-13.1 (1H, br s) 7.60-7.48 (1H, m)
10 7.38-7.33 (1H, m) 7.32-7.22 (2H, m) 7.17-7.08 (3H, m) 7.08-7.00 (2H, m) 6.82
(1H, ddd, *J* = 9.0, 2.8, 1.5 Hz) 4.69 (1H, septet, *J* = 6.0 Hz) 3.15 (3H, s) 1.33 (6H,
d, *J* = 6.0 Hz) 0.97 (9H, s).

Example 63

15 3-Acetylamino-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-
carboxylic acid

(a) 3-Acetylamino-5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid
ethyl ester

20 The subtitle product was prepared in accordance with Example 52 step (b) from
5-benzyloxy-3-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester
(see Example 57 step (b)) and acetamide.

(b) 3-(Acetyl-*tert*-butoxycarbonylamino)-5-benzyloxy-1-(4-isopropoxyphenyl)-
25 indole-2-carboxylic acid ethyl ester

(Boc)₂O (1.09g, 5.87 mmol) and DMAP (144 mg, 1.17 mmol) were added to a
stirred suspension of 3-acetylamino-5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-
carboxylic acid ethyl ester (571 mg, 1.17 mmol, see step (a) above), Et₃N (200 μL,
1.17 mmol) in CH₂Cl₂. The mixture was stirred at 40 °C for 24 h, poured into HCl
30 (aq, 0.5 M) and extracted with CH₂Cl₂. The combined extracts were washed with
NaHCO₃ (aq, sat) and water, dried (Na₂SO₄), concentrated and purified by
chromatography to give the sub-title compound (587 mg, 88%).

(c) 3-(Acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester

The sub-title product was prepared in accordance to Example 23 step (d) from
5 3-(acetyl-*tert*-butoxycarbonylamino)-5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (b) above).

(d) 3-(Acetyl-*tert*-butoxycarbonylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester

10 The sub-title compound was prepared in accordance with Example 1 step (c) from 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (c) above) and 4-trifluoromethoxyphenylboronic acid.

15 (e) 3-Acetylamino-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester

HCl (4 M in dioxane, 0.35 mL, 0.36 mmol) was added to a stirred solution of 3-(acetyl-*tert*-butoxycarbonylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid ethyl ester (231 mg, 0.36 mmol) in CH₂Cl₂
20 (10 mL). The mixture was stirred at rt for 2 h. HCl (aq, conc, 0.3 mL) was added and stirring was continued for 2 h. The volatiles were removed and water (20 mL) was added. The mixture was extracted with EtOAc. The combined extracts were washed with NaHCO₃ (aq, sat) and water, dried (Na₂SO₄), concentrated and purified by chromatography to give the sub-title compound (170 mg, 87%).

25

(f) 3-Acetylamino-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 23 step (f) from 3-acetylamino-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)indole-2-
30 carboxylic acid ethyl ester (see step (e) above).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 0.6 (1H, s) 7.48 (1H, s) 7.24 (2H, d, J = 8.8 Hz) 7.23 (2H, d, J = 8.8 Hz) 7.07-6.96 (6H, m) 4.67 (1H, septet, J = 6.0 Hz) 2.08 (3H, s) 1.32 (6H, d, J = 6.0 Hz).

5 Example 64

3-Acetylamino-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (c)) and 4-trifluoromethylphenylboronic acid, followed by the removal of the Boc-group (see Example 63 step (e)) and hydrolysis (see Example 23 step (f)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 10.61 (1H, s) 7.74-7.63 (3H, m) 7.21 (2H, d, J = 8.8 Hz) 7.06 (2H, d, J = 8.8 Hz) 7.03-6.95 (4H, m) 4.66 (1H, septet, J = 6.0 Hz) 2.08 (3H, s) 1.32 (6H, d, J = 6.0 Hz).

Example 65

3-Acetylamino-5-(2,2-difluorobenzo[1,3]dioxol-5-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

20 The title compound was prepared in accordance with Example 1 step (c) from 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (c)) and 2,2-difluorobenzo[1,3]dioxole-5-boronic acid (see Example 35 step (a)), followed by removal of the Boc-group (see Example 63 step (e)) and hydrolysis (see Example 23 step (f)).

25 200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 9.79 (1H, br s) 7.36 (1H, d, J = 9.0 Hz) 7.34-7.30 (1H, m) 7.28-7.19 (2H, m) 7.16 (1H, d, J = 2.4 Hz) 7.07-6.99 (4H, m) 6.72 (1H, dd, J = 9.0, 2.4 Hz) 4.68 (1H, septet, J = 6.0 Hz) 2.08 (3H, s) 1.32 (6H, d, J = 6.0 Hz).

Example 663-Acetylamino-5-(4-chloro-3-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from
5 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (c)) and 4-chloro-3-trifluoromethoxyphenyl boronic acid (see Example 14, step (b)), followed by removal of the Boc-group (see Example 63 step (e)) and hydrolysis (see Example 23 step (f)).

10 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 9.84-9.74 (1H br s) 7.64 (1H, d, *J* = 9.0 Hz) 7.43-7.39 (1H, m) 7.30-7.21 (2H, m) 7.20-7.16 (1H, m) 7.10-7.00 (4H, m) 6.95 (1H, dd, *J* = 9.0, 2.8 Hz) 4.68 (1H, septet, *J* = 6.0 Hz) 2.09 (3H, s) 1.32 (6H, d, *J* = 6.0 Hz).

15 Example 673-Acetylamino-1-(4-isopropoxyphenyl)-5-(4-isopropoxy-3-trifluoromethoxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from
20 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (c)) and 4-isopropoxy-3-trifluoromethoxyphenyl boronic acid (Example 34 step (a-c)), followed by removal of the Boc-group (see Example 63 step (e)) and hydrolysis (see Example 23 step (f)).

25 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.2-12.7 (1H, br s) 10.0 (1H, br s) 7.39-7.34 (1H, m) 7.28-7.18 (3H, m) 7.07-6.96 (5H, m) 6.91 (1H, dd, *J* = 9.0, 2.9 Hz) 4.67 (1H, septet, *J* = 6.0 Hz) 4.59 (1H, septet, *J* = 6.0 Hz) 2.07 (3H, s) 1.32 (6H, d, *J* = 6.0 Hz) 1.25 (6H, d, *J* = 6.0 Hz).

Example 683-Acetylamino-5-(benzo[1,3]dioxol-5-yloxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid5 (a) Benzo[1,3]dioxole-5-boronic acid

The sub-title compound was prepared in accordance with Example 14 step (b) from 5-bromobenzo[1,3]dioxole.

(b) The title compound was prepared in accordance with Example 1 step (c) from
10 3-(acetyl-*tert*-butoxycarbonylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (c)) and benzo[1,3]dioxole-5-boronic acid (see step (a) above), followed by removal of the Boc-group (see Example 63 step (e)) and hydrolysis (see Example 23 step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 11.1-10.9 (1H, br s) 7.65 (1H, s) 7.19-7.10
15 (2H, m) 7.03-6.93 (2H, m) 6.91-6.87 (2H, m) 6.84 (1H, d, *J* = 8.4 Hz) 6.61 (1H, d, *J* = 2.5 Hz) 6.35 (1H, dd, *J* = 8.4, 2.5) 6.0 (2H, s) 4.64 (1H, septet, *J* = 6.0 Hz) 2.07 (3H, s) 1.31 (6H, d, *J* = 6.0 Hz).

Example 6920 3-(Acetylmethylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)-indole-2-carboxylic acid(a) 3-(Acetylmethylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

25 The sub-title compound was prepared in accordance Example 60 step (a) and (b) from 3-acetylamino-5-benzyloxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 63 step (a)).

30 (b) 3-(Acetylmethylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from 3-(acetylmethylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic

acid ethyl ester (see step (a) above) and 4-trifluoromethylphenylboronic acid followed by hydrolysis (see Example 23 step (f)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.76-7.65 (2H, m) 7.42-7.25 (3H, m) 7.21-6.98 (6H, m) 4.69 (1H, septet, $J = 6.0$ Hz) 3.15 (3H, s) 1.79 (3H, s) 1.32 (6H, d, $J = 6.0$ Hz).

Example 70

3-(Acetylmethylamino)-1-(4-isopropoxyphenyl)-5-(4-trifluoromethoxyphenoxy)-indole-2-carboxylic acid

10 The title compound was prepared in accordance with Example 1 step (c) from 3-(acetylmethylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 69 step (a)) and 4-trifluoromethoxyphenylboronic acid followed by hydrolysis (see Example 23 step (f)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.75-7.66 (2H, m) 7.39-7.29 (3H, m) 7.17-7.07 (4H, m) 7.07-6.99 (2H, m) 4.69 (1H, septet, $J = 6.0$ Hz) 3.16 (3H, s) 1.80 (3H, s) 1.33 (6H, d, $J = 6.0$ Hz).

Example 71

3-(Acetylmethylamino)-5-(benzo[1,3]dioxol-5-yloxy)-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid

20 The title compound was prepared in accordance with Example 1 step (c) from 3-(acetylmethylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 69 step (a)) and benzo[1,3]dioxole-5-boronic acid (see Example 68 step (a)) followed by hydrolysis (see Example 23 step (f)).

25 200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 3.2 (1H, s) 7.36-7.25 (2H, m) 7.15-6.98 (5H, m) 6.88 (1H, d, $J = 8.4$ Hz) 6.73 (1H, d, $J = 2.4$ Hz) 6.46 (1H, dd, $J = 8.4, 2.4$ Hz) 6.03 (2H, s) 4.63 (1H, septet, $J = 6.0$ Hz) 3.13 (3H, s) 1.77 (3H, s) 1.32 (6H, d, $J = 6.0$ Hz).

Example 72

3-(Acetylmethylamino)-5-(4-chloro-3-trifluoromethoxyphenoxy)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 1 step (c) from
5 3-(acetylmethylamino)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic
acid ethyl ester (see Example 69 step (a)) and 4-chloro-3-trifluoromethoxyphenyl
boronic acid (see Example 14, step (b)) followed by hydrolysis (see Example 23
step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.64 (1H, d, *J* = 9.0 Hz) 7.36-7.27 (2H, m)
10 7.25 (1H, d, *J* = 0.9 Hz) 7.19-7.12 (2H, m) 7.08-6.97 (4H, m) 4.67 (1H, septet, *J*
= 6.0 Hz) 3.14 (3H, s) 1.79 (3H, s) 1.32 (6H, d, *J* = 6.0 Hz).

Example 73

1-(4-Isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-6-(3-trifluoromethoxy-
15 phenoxy)indole-2-carboxylic acid

(a) 3-Bromo-1-(4-isopropoxyphenyl)-6-(3-trifluoromethoxyphenoxy)indole-2-
carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 52 step (a)
20 from 1-(4-isopropoxyphenyl)-6-(3-trifluoromethoxyphenoxy)indole-2-carboxylic
acid ethyl ester (see Example 24) followed by bromination with NBS (see
Example 52 step (a)).

(b) 1-(4-Isopropoxyphenyl)-3-[(pyridine-3-carbonyl)amino]-6-(3-trifluorometh-
25 oxyphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 53 step (a) from
3-bromo-1-(4-isopropoxyphenyl)-6-(3-trifluoromethoxyphenoxy)indole-2-
carboxylic acid ethyl ester (see step (a) above) followed by hydrolysis (see
Example 23 step (f)).

30 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.1 (1H, br s) 10.59 (1H, s) 9.21 (1H, d, *J*
= 1.2 Hz) 8.83-8.78 (1H, m) 8.42-8.34 (1H, m) 7.86 (1H, d, *J* = 8.8 Hz) 7.62 (1H,
ddd, *J* = 8.0, 4.8, 0.5 Hz) 7.39-7.30 (2H, m) 7.29-7.21 (2H, m) 7.12-6.98 (4H, m)

6.95 (1H, dd, $J = 8.8, 2.0$ Hz) 6.60 (1H, d, $J = 2.0$ Hz) 4.66 (1H, septet, $J = 6.0$ Hz) 1.28 (6H, d, $J = 6.0$ Hz).

Example 74

5 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-6-(3-trifluoromethylphenoxy)indole-2-carboxylic acid

(a) 3-Bromo-1-(4-isopropoxyphenyl)-6-(3-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester

10 The sub-title compound was prepared in accordance with Example 1 step (c) from 6-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see Example 23 step (d)) and 3-trifluoromethylphenylboronic acid followed by bromination with NBS (see Example 52 step (a)).

15 (b) 3-(2,2-Dimethylpropionylamino)-1-(4-isopropoxyphenyl)-6-(3-trifluoromethylphenoxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 53 step (a) from 3-bromo-1-(4-isopropoxyphenyl)-6-(3-trifluoromethylphenoxy)indole-2-carboxylic acid ethyl ester (see step (a) above) and 2,2-dimethylpropionamide
20 followed by hydrolysis (see Example 23 step (f)).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.1 (1H, br s) 9.74 (1H, s) 7.93 (1H, d, $J = 8.8$ Hz) 7.63-7.52 (1H, m) 7.47-7.40 (1H, m) 7.28-7.18 (4H, m) 7.03-6.95 (2H, m) 6.91 (1H, dd, $J = 8.8, 2.2$ Hz) 6.59 (1H, d, $J = 2.2$ Hz) 4.64 (1H, septet, $J = 6.0$ Hz) 1.30 (9H, s) 1.29 (6H, d, $J = 6.0$ Hz).

Example 753-(2-Cyanoethyl)-1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

- 5 (a) 5-Benzyloxy-3-(2-cyanovinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-benzyloxy-3-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (2.2 g, 3.96 mmol; see Example 57, step (b)), NaOAc (1.3 g, 16 mmol), PdCl₂(PPh₃)₂ (140 mg, 0.2 mmol), acrylonitrile (1.1 ml, 16 mmol), Et₃N (0.7 mL, 5 mmol) and DMF (10 mL) was stirred under argon at 70 °C for 7 h. The mixture was allowed to cool to rt, diluted with EtOAc, washed with water, brine and NaHCO₃ (aq, sat), dried (Na₂SO₄), concentrated and purified by chromatography to give the sub-title compound (1.72 g, 90%).

- 15 (b) 3-(2-Cyanoethyl)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 23 step (d) from 5-benzyloxy-3-(2-cyanovinyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (see step (a) above).

20

- (c) 3-(2-Cyanoethyl)-1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yl-oxy)indole-2-carboxylic acid ethyl ester

A mixture of 3-(2-cyanoethyl)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (100 mg, 0.25 mmol, see step (b) above), 2-chloro-5-trifluoromethylpyridine (49 mg, 0.26 mol), K₂CO₃ (173 mg, 1.25 mmol), 18-crown-6 (7 mg, 0.025 mmol) and DMF (2 mL) was stirred at 50 °C for 40 hours. The mixture was diluted with EtOAc, washed with NaHCO₃ (aq, sat) and dried (Na₂SO₄). Concentration and purification by chromatography gave the sub-title compound (110 mg, 80%).

30

(d) 3-(2-Cyanoethyl)-1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yl-oxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 23 step (f) from 3-(2-cyanoethyl)-1-(4-isopropoxyphenyl)-5-(5-trifluoromethylpyridin-2-yloxy)-indole-2-carboxylic acid ethyl ester (see step (c) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 8.55 (1H, br s) 8.23 (1H, dd, *J* = 8.9, 2.3 Hz) 7.76 (1H, d, *J* = 2.0 Hz) 7.30-7.18 (3H, m) 7.13 (1H, dd, *J* = 9.0 Hz) 7.08-6.98 (3H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 3.45-3.29 (m, 2H, overlapped with water) 2.82 (1H, t, *J* = 7.3 Hz) 1.33 (6H, d, *J* = 6.0 Hz)

Example 76

5-(6-Chloropyridin-2-yloxy)-3-(2-cyanoethyl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 75 step (c) from 3-(2-cyanoethyl)-5-hydroxy-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester and 2,6-dichloropyridine (see Example 75 step (b)), followed by hydrolysis (see Example 23, step (f)).

200 MHz ¹H-NMR (CDCl₃, ppm) δ 7.62 (1H, t, *J* = 7.8 Hz) 7.54-7.46 (1H, m) 7.27-6.92 (7H, m) 6.78 (1H, d, *J* = 8.4 Hz) 4.63 (1H, septet, *J* = 6.0 Hz) 3.48 (2H, t, *J* = 7.3 Hz) 2.78 (2H, t, *J* = 7.3 Hz) 1.41 (6H, d, *J* = 6.0 Hz)

Example 77

1-(4-Isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

(a) 5-Hydroxy-1-(4-isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 53, step (a) from 5-benzyloxy-3-iodo-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (Example 57, step (b)), followed by removal of the *O*-benzyl group (see Example 23, step (d)).

(b) 1-(4-Isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)-5-(5-trifluoromethylpyridin-2-yloxy)indole-2-carboxylic acid

The title compound was prepared in accordance with Example 75, step (c) from 5-hydroxy-1-(4-isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid ethyl ester (see step (a) above) and 2-chloro-5-trifluoromethylpyridine, followed by hydrolysis (see Example 23, step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 8.52 (1H, s) 8.27-8.14 (1H, m) 7.40-6.94 (8H, m) 4.67 (1H, septet, *J* = 5.9 Hz); 3.93-3.75 (2H, m) 2.6-2.3 (2H, m, overlapped with DMSO) 2.21-2.02 (2H, m) 1.32 (6H, d, *J* = 5.9 Hz).

Example 78

5-(6-Chloropyridin-2-yloxy)-1-(4-isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)-indole-2-carboxylic acid

The title compound was prepared in accordance with Example 75, step (c) from 5-hydroxy-1-(4-isopropoxyphenyl)-3-(2-oxopyrrolidin-1-yl)indole-2-carboxylic acid ethyl ester and 2,6-dichloropyridine (see Example 77, step (a)), followed by hydrolysis (see Example 23, step (f)).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.92-7.81 (1H, m) 7.37-7.16 (4H, m) 7.13-6.91 (m, 5H) 4.68 (1H, septet, *J* = 5.9 Hz) 3.83 (2H, t, *J* = 6.7 Hz) 2.55-2.30 (2H, m, overlapped with DMSO) 2.23-2.05 (2H, m) 1.32 (6H, d, *J* = 5.9 Hz).

Example 79

3-Chloro-1-(4-cyclopentyloxyphenyl)-5-phenylethynylindole-2-carboxylic acid

(a) 3-Chloro-1-(4-cyclopentyloxyphenyl)-5-phenylethynylindole-2-carboxylic acid ethyl ester

A mixture of 5-bromo-3-chloro-1-(4-cyclopentyloxyphenyl)indole-2-carboxylic acid ethyl ester (690 mg, 1.5 mmol; see Example 39, step (c)), trimethylphenylethynylstannane (776 mg, 3.0 mg), Pd[(PPh₃)₄] (27 mg, 0.023 mmol), Ph₃P (6.0 mg, 0.023 mmol) and anhydrous toluene (4.0 mL) was heated under argon at 110 °C for 12 h, whereupon the color changed from cloudy yellow to black. After dilution with EtOAc (30 mL), the mixture was washed with NH₄Cl (aq, 10%),

brine and dried (Na_2SO_4). Concentration and purification by chromatography afforded the sub-title compound (300 mg, 42% yield).

(b) 3-Chloro-1-(4-cyclopentyloxyphenyl)-5-phenylethynylindole-2-carboxylic acid

The title compound was prepared in accordance with Example 23, step (f) from 3-chloro-1-(4-cyclopentyloxyphenyl)-5-phenylethynylindole-2-carboxylic acid ethyl ester (see step (a) above).

200 MHz ^1H -NMR ($\text{DMSO}-d_6$, ppm) δ 13.55-13.35 (1H, br s) 7.90 (1H, d, $J = 1.1$ Hz) 7.63-7.42 (6H, m) 7.36-7.30 (2H, m) 7.10 (1H, d, $J = 8.7$ Hz) 7.07-7.00 (2H, m) 4.95-4.86 (1H, m) 2.03-1.57 (8H, m).

Example 80

3-Chloro-1-(4-isopropoxyphenyl)-5-piperidin-1-ylindole-2-carboxylic acid

15

(a) 5-Bromo-3-chloroindole-2-carboxylic acid ethyl ester

A mixture of 5-bromoindole-2-carboxylic acid ethyl ester (4.00 g, 14.9 mmol), SO_2Cl_2 (1.8 mL, 22.4 mmol) and benzene (125 mL) was stirred at 90 °C for 2.5 h, and cooled to rt. NaHCO_3 (aq, sat) was added and the mixture was extracted with EtOAc. The combined extracts were washed with water and brine and dried (Na_2SO_4). Concentration and crystallisation from toluene gave the sub-title compound (3.87 g 85 %).

(b) 5-Bromo-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

Anhydrous CH_2Cl_2 (80 mL), Et_3N (3.36 mL, 23.9 mmol) and pyridine (1.95 mL, 23.9 mmol) were added to 5-bromo-3-chloroindole-2-carboxylic acid ethyl ester (3.60 g, 11.9 mmol; see step (a) above), $\text{Cu}(\text{OAc})_2$ (4.34 g, 23.9 mmol), 3 Å molecular sieves (ca. 7 g) and 4-cyclopentyloxyphenylboronic acid (4.30 g, 23.9 mmol). The mixture was stirred vigorously at rt for 48 h, and additional Et_3N (1.6 mL, 11.0 mmol), pyridine (0.90 mL, 11.0 mmol), $\text{Cu}(\text{OAc})_2$ (2.00 g, 11.0 mmol) and 4-cyclopentyloxyphenylboronic acid (2.27 g, 11.0 mmol) were added. The mixture was stirred at rt for 48 h and filtered through Celite®. The solids were

washed with EtOAc and the combined filtrates were washed with NH_4OH (aq), HCl (aq, 0.1 M) and brine, dried (Na_2SO_4), concentrated and purified by chromatography to afford the sub-title compound (4.40 g, 85%).

5 (c) 3-Chloro-1-(4-isopropoxyphenyl)-5-piperidin-1-ylindole-2-carboxylic acid ethyl ester

A mixture of 5-bromo-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (198 mg, 0.45 mmol) (step (b) above), $\text{Pd}_2(\text{dba})_3$ (20.6 mg, 0.023 mmol), BINAP (42 g, 0.068 mmol), piperazine (55 μL , 0.56 mmol) Cs_2CO_3 (205mg, 0.63 mmol) and toluene (2 mL) was stirred at 80 °C for 24 h. The mixture was cooled to rt and filtered through Celite® and the solids were washed with EtOAc. The combined filtrates were washed with water, brine, dried (Na_2SO_4), concentrated and purified by chromatography to afford the sub-title compound (75mg, 37%).

15

(d) 3-Chloro-1-(4-isopropoxyphenyl)-5-piperidin-1-ylindole-2-carboxylic acid

A mixture of 3-chloro-1-(4-isopropoxyphenyl)-5-piperidin-1-ylindole-2-carboxylic acid ethyl ester (75 mg, 0.17 mmol; see step (c)), NaOH (34 mg, 0.85 mmol), water (1.0 mL) and EtOH (2.0 mL) was stirred at 120 °C for 30 min. After cooling, the mixture was acidified with HCl (aq, 1 M) to pH 5 and extracted with EtOAc. The combined extracts were washed with brine and dried (Na_2SO_4). Concentration and purification by chromatography gave the title compound (60 mg, 85%).

200 MHz ^1H -NMR ($\text{DMSO}-d_6$, ppm) δ 13.1 (1H, br s) 7.26-7.16 (2H, m) 7.12 (1H, dd, $J = 9.2, 2.0$ Hz) 7.06-6.95 (2H, m) 6.93 (1H, d, $J = 2.0$ Hz) 6.90 (1H, d, $J = 9.2$ Hz) 4.64 (1H, septet, $J = 6.0$ Hz) 3.12-3.00 (4H, m) 1.72-1.42 (6H, m) 1.30 (6H, d, $J = 6.0$ Hz).

Example 815-(5-*tert*-Butyl-2-oxocyclohexyl)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid5 (a) 5-(5-*tert*-Butyl-2-oxocyclohexyl)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester

To a mixture of 5-bromo-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (600 mg, 1.37 mmol) (step (b) in Example 80), 4-*tert*-butylcyclohexanone (848 mg, 5.5 mmol) and K₃PO₄ (1.20 g, 5.6 mmol) and
 10 toluene (0.3 mL), was added a solution of Pd₂(dba)₃ (6.18 mg, 0.0068 mmol) and xantphos (7.81 mg, 0.0136 mmol) in toluene (0.3 mL). The mixture was stirred at 80 °C for 23 h, cooled to rt, diluted with EtOAc, washed with water and brine, dried (Na₂SO₄), concentrated and purified by chromatography to afford the sub-
 title compound (292 mg, 41%).

15

(b) 5-(5-*tert*-Butyl-2-oxocyclohexyl)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

A mixture of 5-(5-*tert*-butyl-2-oxocyclohexyl)-3-chloro-1-(4-isopropoxyphenyl)-indole-2-carboxylic acid ethyl ester (290 mg, 0.57 mmol; see step (a) above),
 20 NaOH (136 mg, 3.41 mmol), water (60 mL) and EtOH (40 mL) was stirred at reflux for 2 h. After cooling, the EtOH was partly evaporated and the mixture was acidified with HCl (aq, 1M) to pH 5 and extracted with EtOAc. The combined extracts were washed with brine and dried (Na₂SO₄). Concentration and purification by chromatography gave the title compound (165 mg, 60%).

25 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ for the major diastereomer 13.3 (1H, br s) 7.44 (1H, s) 7.28-7.24 (2H m) 7.13 (1H, d, *J* = 8.7 Hz) 7.05-7.01 (2H, m) 6.97 (1H, d, *J* = 8.7 Hz) 4.68 (1H, septet, *J* = 6.0 Hz) 3.97-3.92 (1H, m) 2.58 (1H, td, *J* = 14.0, 6.0 Hz) 2.36-2.30 (1H, m) 2.15-2.03 (2H, m) 1.84-1.76 (2H, m) 1.62-1.54 (1H, m) 1.32 (6H, d, *J* = 6.0 Hz) 0.92 (9H, s)

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Example 825-(5-*tert*-Butyl-2-hydroxycyclohexyl)-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid

NaBH₄ (92 mg, 1.0 mmol) was added in portions to a mixture of 5-(5-*tert*-butyl-2-oxo-cyclohexyl)-3-chloro-1-(4-isopropoxyphen-yl)indole-2-carboxylic acid (102 mg, 0.21 mmol; see step (b) in Example 81) water (6 mL) and EtOH (10 mL). After 20 min the mixture was acidified with HCl (aq, 1 M) to pH 1 and stirred for an additional 60 min. The EtOH was partly evaporated and the mixture was extracted with EtOAc. The combined extracts were washed with brine and dried (Na₂SO₄). Concentration and purification by chromatography gave the title compound (165 mg, 60%).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ for the major diastereomer 13.2-13.0 (1H, br s) 7.48 (1H, s) 7.32-7.20 (3H m) 7.08-6.92 (3H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 4.30-4.23 (1H, m) 3.58-3.50 (1H, m) 2.04-2.67 (1H, m) 1.80-1.70 (2H, m) 1.58-1.37 (1H, m) 1.32 (6H, d, *J* = 6.0 Hz) 1.30-1.10 (4H, m) 0.84 (9H, s)

Example 833-Chloro-1-(4-isopropoxyphenyl)-5-(2-phenylcyclopropyl)indole-2-carboxylic acid

20

(a) 4,4,5,5-Tetramethyl-2-(2-phenylcyclopropyl)-[1,3,2]dioxaborolane

Diazomethane (2 g, 47 mmol) in Et₂O (100 mL) was added over 2 h to 4,4,5,5-tetramethyl-2-((*E*)-styryl)-[1,3,2]dioxaborolane (0.8 g, 3.5 mmol), Pd(OAc)₂ (45 mg, 0.2 mmol) and Et₂O (1.0 mL) at 0 °C. The mixture was stirred for 2 h at rt, filtered through Celite[®], concentrated and purified by chromatography to afford the sub-title compound (625 mg, 80%).

(b) Potassium 2-phenyl-cyclopropyltrifluoroborate

A mixture of 4,4,5,5-tetramethyl-2-(2-phenylcyclopropyl)-[1,3,2]dioxaborolane (300 mg, 1.23 mmol; see step (a) above), KHF₂ (670 mg, 8.6 mmol), water (1 mL) and MeOH (4 mL) was stirred at rt for 4 h. The mixture was concentrated and the residue treated with MeCN. The mixture was filtered and concentrated. The

residue was treated with Et₂O and filtered to afford 224 mg (81%) of the sub-title compound.

5 (c) 3-Chloro-1-(4-isopropoxyphenyl)-5-(2-phenylcyclopropyl)indole-2-carboxylic acid ethyl ester

A mixture of 5-bromo-3-chloro-1-(4-isopropoxyphenyl)indole-2-carboxylic acid ethyl ester (218 mg, 0.5 mmol) (step (b) in Example 80), potassium 2-phenylcyclopropyltrifluoroborate (132 mg, 0.6 mmol) (step (b) above), Pd(PPh₃)₄ (29 mg, 0.025 mmol), K₃PO₄ (254 mg, 1.23 mmol), toluene (1.5 mL) and water was
10 stirred at 110 °C for 17 h. The mixture was cooled to rt, diluted with EtOAc and washed with HCl (aq, 0.1 M), NaHCO₃ (aq, sat), water, brine and dried (Na₂SO₄). Concentration and purification by chromatography gave the sub-title compound (74mg, 31%).

15 (d) 3-Chloro-1-(4-isopropoxyphenyl)-5-(2-phenylcyclopropyl)indole-2-carboxylic acid

The title compound was prepared in accordance with step ((b) in Example 81) from 3-chloro-1-(4-isopropoxyphenyl)-5-(2-phenylcyclopropyl)indole-2-carboxylic acid ethyl ester (see step (c) in above).

20 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.3-13.1 (1H, br s) 7.46 (1H, s) 7.36-7.10 (8H, m) 7.09-6.92 (3H, m) 4.68 (1H, septet, *J* = 6.0 Hz) 2.43-2.30 (1H, m) 2.28-2.13 (1H, m) 1.59-1.40 (2H, m) 1.32 (6H, d, *J* = 6.1 Hz)

Example 84

25 The following compounds are prepared in accordance with techniques described herein:

- 3-chloro-5-cyclohexyl-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-5-(norbornan-2-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-5-cyclopropyl-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 30 3-chloro-5-(cyclopenten-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-5-(5,5-dimethylcyclohexen-3-one-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;

- 3-chloro-5-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydropyrid-6-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-cyclohexyl-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-(norbornan-2-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 5 3-chloro-6-cyclopropyl-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-(cyclopenten-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-(5,5-dimethylcyclohexen-3-one-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-(1-*tert*-butoxycarbonyl-1,2,3,4-tetrahydropyrid-6-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 10 3-chloro-5-(pyrrolidin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-5-(morpholin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-5-(4-cyclopentylpiperazin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 15 3-chloro-6-(pyrrolidin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid;
- 3-chloro-6-(morpholin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid; and
- 3-chloro-6-(4-cyclopentylpiperazin-1-yl)-1-(4-isopropoxyphenyl)indole-2-carboxylic acid.

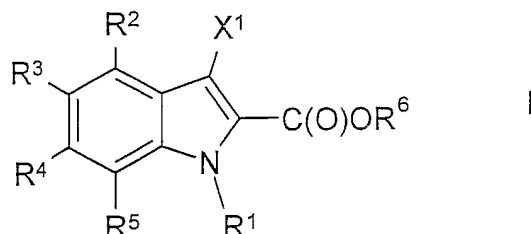
20 Example 85

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 μ M or below. For example, the following representative compounds of the examples exhibited the following IC₅₀ values:

- 25 Example 1: 430 nM
- Example 10: 240 nM
- Example 13: 3700 nM
- Example 21: 75 nM
- Example 40: 610 nM

Claims

1. A compound of formula I,



wherein

- one of the groups R^2 , R^3 , R^4 and R^5 represents -D-E, a cycloalkyl group or a heterocycloalkyl group (which latter two groups are optionally substituted by one or more substituents selected from G^1 and/or Z^1) and:

- a) the other groups are independently selected from hydrogen, G^1 , 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, in the case when one of R^2 , R^3 , R^4 and R^5 represents -D-E, an aryl group and a heteroaryl group (which latter two groups are optionally substituted by one or more substituents selected from A); 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, which ring is itself optionally substituted by one or more substituents selected from halo, $-R^6$, $-OR^6$ and $=O$;

D represents $-O-$, $-C(R^7)(R^8)-$, C_{2-4} alkylene, $-C(O)-$ or $-S(O)_m-$;

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

R^7 and R^8 independently represent H, halo or C_{1-6} alkyl, which latter group is optionally substituted by halo, or R^7 and R^8 may together form, along with the carbon atom to which they are attached, a 3- to 6-membered ring, which ring optionally contains a heteroatom and is optionally substituted by one or more substituents selected from halo and C_{1-3} alkyl, which latter group is optionally substituted by one or more halo substituents;

X^1 represents H, halo, $-N(R^9)-J-R^{10}$ or $-Q-X^2$;

J represents a single bond, $-C(O)-$ or $-S(O)_m-$;

Q represents a single bond, $-O-$, $-C(O)-$ or $-S(O)_m-$;

m represents 0, 1 or 2;

15

X^2 represents:

- (a) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from A; or
- (b) 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 ;

20

R^6 , R^9 and R^{10} independently represent:

- 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 ; or
- R^9 and R^{10} may be linked together to form, along with the N atom and the J group to which R^9 and R^{10} are respectively attached, a 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^1 and/or Z^1 ;

30

A represents:

- I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B;
- II) C₁₋₈ alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G¹ and/or Z¹; or
- III) a G¹ group;

G¹ represents halo, cyano, -N₃, -NO₂, -ONO₂ or -A¹-R^{11a};

wherein A¹ represents a single bond or a spacer group selected from -C(O)A²-, -S(O)₂A³-, -N(R^{12a})A⁴- or -OA⁵-, in which:

A² represents a single bond, -O-, -N(R^{12b})- or -C(O)-;

A³ represents a single bond, -O- or -N(R^{12c})-;

A⁴ and A⁵ independently represent a single bond, -C(O)-, -C(O)N(R^{12d})-, -C(O)O-, -S(O)₂- or -S(O)₂N(R^{12e})-;

Z¹ represents =O, =S, =NOR^{11b}, =NS(O)₂N(R^{12f})R^{11c}, =NCN or =C(H)NO₂;

B represents:

- I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G²;
- II) C₁₋₈ alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G² and/or Z²; or
- III) a G² group;

G² represents halo, cyano, -N₃, -NO₂, -ONO₂ or -A⁶-R^{13a};

wherein A⁶ represents a single bond or a spacer group selected from -C(O)A⁷-, -S(O)₂A⁸-, -N(R^{14a})A⁹- or -OA¹⁰-, in which:

A⁷ represents a single bond, -O-, -N(R^{14b})- or -C(O)-;

A⁸ represents a single bond, -O- or -N(R^{14c})-;

A⁹ and A¹⁰ independently represent a single bond, -C(O)-, -C(O)N(R^{14d})-, -C(O)O-, -S(O)₂- or -S(O)₂N(R^{14e})-;

Z^2 represents $=O$, $=S$, $=NOR^{13b}$, $=NS(O)_2N(R^{14f})R^{13c}$, $=NCN$ or $=C(H)NO_2$;

R^{11a} , R^{11b} , R^{11c} , R^{12a} , R^{12b} , R^{12c} , R^{12d} , R^{12e} , R^{12f} , R^{13a} , R^{13b} , R^{13c} , R^{14a} , R^{14b} , R^{14c} , R^{14d} , R^{14e} and R^{14f} are independently selected from:

- 5 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 ;
- iii) C_{1-8} alkyl or a heterocycloalkyl group, both of which are optionally substituted by G^3 and/or Z^3 ; or
- 10 any pair of R^{11a} to R^{11c} and R^{12a} to R^{12f} , and/or R^{13a} to R^{13c} and R^{14a} to R^{14f} , may 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 ;

15

G^3 represents halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^{11}-R^{15a}$;

wherein A^{11} represents a single bond or a spacer group selected from $-C(O)A^{12}-$, $-S(O)_2A^{13}-$, $-N(R^{16a})A^{14}-$ or $-OA^{15}-$, in which:

A^{12} represents a single bond, $-O-$, $-N(R^{16b})-$ or $-C(O)-$;

- 20 A^{13} represents a single bond, $-O-$ or $-N(R^{16c})-$;

A^{14} and A^{15} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{16d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{16e})-$;

Z^3 represents $=O$, $=S$, $=NOR^{15b}$, $=NS(O)_2N(R^{16f})R^{15c}$, $=NCN$ or $=C(H)NO_2$;

25

R^{15a} , R^{15b} , R^{15c} , R^{16a} , R^{16b} , R^{16c} , R^{16d} , R^{16e} and R^{16f} 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, $-N(R^{17a})R^{18a}$, $-OR^{17b}$ and $=O$; and
- 30

iii) an aryl or heteroaryl group, both of which are optionally substituted by one or more substituents selected from halo, C₁₋₄ alkyl, -N(R^{17c})R^{18b} and -OR^{17d}; or any pair of R^{15a} to R^{15c} and R^{16a} to R^{16f} may 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, C₁₋₄ alkyl, -N(R^{17e})R^{18c}, -OR^{17f} and =O;

R^{17a}, R^{17b}, R^{17c}, R^{17d}, R^{17e}, R^{17f}, R^{18a}, R^{18b} and R^{18c} are independently selected from hydrogen and C₁₋₄ alkyl, which latter group is optionally substituted by one or more halo groups;

or a pharmaceutically-acceptable salt thereof,

provided that, when R³ represents -D-E, in which D represents -C(R⁷)(R⁸)-, X¹, R², R⁴, R⁵, R⁷ and R⁸ all represent H and:

- (a) E represents a 2-butyl-5-hydroxymethyl-1*H*-imidazol-1-yl group, then R⁶ does not represent H when R¹ represents phenyl or 2-carboxyphenyl;
- (b) E represents a 2-butyl-5-hydroxymethyl-1*H*-imidazol-1-yl group or a 2-butyl-5-formyl-1*H*-imidazol-1-yl group, then R⁶ does not represent ethyl when R¹ represents phenyl or 2-ethoxycarbonylphenyl;
- (c) E represents a 2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl group, then R⁶ does not represent H or ethyl when R¹ represents 2-(1*H*-tetrazol-5-yl)phenyl; or
- (d) E represents a 2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl group or a 2-butyl-4-chloro-5-formyl-1*H*-imidazol-1-yl group, then R⁶ does not represent ethyl when R¹ represents 2-cyanophenyl.

2. A compound as claimed in Claim 1, wherein A represents C₁₋₆ alkyl optionally substituted by one or more G¹ groups or G¹.

3. A compound as claimed in Claim 1 or Claim 2, wherein G^1 represents halo, cyano, $-NO_2$ or $-A^1-R^{11a}$.
4. A compound as claimed in Claim 3, wherein, when one of R^2 to R^5 represents -D-E-, then G^1 represents fluoro, chloro, $-NO_2$ or $-A^1-R^{11a}$.
5. A compound as claimed in Claim 3, wherein, when one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group, then G^1 represents fluoro, chloro or $-A^1-R^{11a}$.
- 10 6. A compound as claimed in any one of Claims 1 to 5, wherein, when one of R^2 to R^5 represents -D-E-, then A^1 represents a single bond, $-C(O)O-$, $-N(R^{12a})A^4-$ or $-OA^5-$.
- 15 7. A compound as claimed in any one of the preceding claims, wherein when one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group, then A^1 represents a single bond, $-C(O)O-$, $-C(O)N(R^{12b})-$, $-N(R^{12a})A^4-$ or $-OA^5-$.
- 20 8. A compound as claimed in Claim 7, wherein A^1 represents a single bond, $-C(O)O-$ or $-OA^5-$.
9. A compound as claimed in any one of the preceding claims, wherein A^4 and A^5 independently represent a single bond.
- 25 10. A compound as claimed in any one of the preceding claims, wherein, when one of R^2 to R^5 represents -D-E-, then R^{11a} , R^{11b} and R^{11c} independently represent a phenyl group, a tetrazolyl group, an imidazolyl group, a pyridyl group, or a C_{1-3} alkyl group, all of which are optionally substituted by one or more G^3 groups.
- 30 11. A compound as claimed in any one of Claims 1 to 9, wherein, when one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl group,

then R^{11a} , R^{11b} and R^{11c} independently represent a phenyl group, a tetrazolyl group, a pyridyl group, an imidazolyl group, C_{1-6} alkyl or C_{4-6} heterocycloalkyl, all of which are optionally substituted by one or more halo groups.

- 5 12. A compound as claimed in Claim 11, wherein R^{11a} , R^{11b} and R^{11c} independently represent C_{1-6} alkyl or C_{4-6} heterocycloalkyl, both of which are optionally substituted by one or more halo groups.

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

14. A compound as claimed in any one of the preceding claims, wherein D represents $-CH_2-$, ethylene, $-S-$, $-S(O)-$, $-S(O)_2-$, $-O-$ or $-C(O)-$.

- 15 15. A compound as claimed in Claim 14, wherein D represents $-O-$ or $-C(O)-$.

16. A compound as claimed in any one of the preceding claims, wherein R^1 , E and (when they represent such aryl or heteroaryl groups) X^2 , R^9 and R^{10} represent optionally substituted phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, 20 imidazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, indazolyl, indolyl, indolinyl, isoindolinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, quinoliziny, benzofuranyl, isobenzofuranyl, chromanyl, benzothienyl, pyridaziny, pyrimidinyl, pyraziny, indazolyl, benzimidazolyl, quinazolinyl, quinoxaliny, 1,3-benzodioxolyl, tetrazolyl, benzothiazolyl, and/or 25 benzodioxany, groups.

17. A compound as claimed in Claim 16, wherein R^1 represents optionally substituted phenyl, pyridyl or imidazolyl.

- 30 18. A compound as claimed in Claim 16 or Claim 17, wherein E represents optionally substituted 1,3-benzodioxolyl, phenyl, pyridyl, quinolinyl or imidazolyl.

19. A compound as claimed in Claim 18, wherein E represents phenyl, pyridyl, quinolinyl or imidazolyl.
- 5 20. A compound as claimed in any one of Claims 16 to 19, wherein, when one of R^2 to R^5 represents -D-E-, then the optional substituents are selected from phenyl, =O (in the case of substituents on non-aromatic rings), halo, cyano, -NO₂, C₁₋₆ alkyl (which alkyl group may be linear or branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more halo group),
10 heterocycloalkyl (which heterocycloalkyl group is optionally substituted by one or more substituents selected from C₁₋₃ alkyl and =O), -OR¹⁹ and -N(R¹⁹)R²⁰, wherein R¹⁹ and R²⁰ independently represent H or C₁₋₆ alkyl (which alkyl group is optionally substituted by one or more halo groups).
- 15 21. A compound as claimed in Claim 20, wherein the optional substituents are selected from halo, cyano, -NO₂, C₁₋₆ alkyl (which alkyl group may be linear or branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more halo group), heterocycloalkyl (which heterocycloalkyl group is optionally substituted by one or more substituents selected from C₁₋₃ alkyl and =O), -OR¹⁹
20 and -N(R¹⁹)R²⁰, wherein R¹⁹ and R²⁰ independently represent H or C₁₋₆ alkyl (which alkyl group is optionally substituted by one or more halo groups).
22. A compound as claimed in any one of Claims 16 to 19, wherein, when one of R^2 to R^5 represents an optionally substituted cycloalkyl or heterocycloalkyl
25 group, then the optional substituents are selected from phenyl, =O (in the case of substituents on non-aromatic rings), halo, cyano, -NO₂, C₁₋₆ alkyl (which alkyl group may be linear or branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more halo group), heterocycloalkyl (which heterocycloalkyl group is optionally substituted by one or more substituents
30 selected from C₁₋₃ alkyl and =O), -OR¹⁹, -N(R¹⁹)R²⁰ and -C(O)OR¹⁹, wherein R¹⁹ and R²⁰ independently represent H or C₁₋₆ alkyl (which alkyl group is optionally substituted by one or more halo groups).

23. A compound as claimed in Claim 22, wherein the optional substituents are selected from halo, cyano, $-\text{NO}_2$, 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), heterocycloalkyl (which heterocycloalkyl group is optionally substituted by one or more substituents selected from C_{1-3} alkyl and $=\text{O}$), $-\text{OR}^{19}$, $-\text{N}(\text{R}^{19})\text{R}^{20}$ and $-\text{C}(\text{O})\text{OR}^{19}$, wherein R^{19} and R^{20} independently represent H or C_{1-6} alkyl (which alkyl group is optionally substituted by one or more halo groups).
24. A compound as claimed in any one of the preceding claims, wherein X^1 represents $-\text{N}(\text{R}^9)-\text{J}-\text{R}^{10}$, C_{1-3} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by $-\text{N}(\text{R}^{12a})\text{R}^{11a}$ -, $-\text{OR}^{11a}$ -, $-\text{R}^{11a}$ or halo), H or halo.
25. A compound as claimed in Claim 24, wherein X^1 represents C_{1-3} alkyl, heterocycloalkyl (which latter two groups are optionally substituted by $-\text{N}(\text{R}^{12a})\text{R}^{11a}$ -, $-\text{OR}^{11a}$ -, $-\text{R}^{11a}$ or halo), H or halo.
26. A compound as claimed in any one of the preceding claims, wherein J represents $-\text{C}(\text{O})$ - or $-\text{S}(\text{O})_2$ -.
27. A compound as claimed in any one of the preceding claims, wherein one of R^4 and R^3 represents $-\text{D-E}$ or an optionally substituted cycloalkyl or heterocycloalkyl group and the other represents H.
28. A compound as claimed in Claim 27, wherein R^3 represents $-\text{D-E}$.
29. A compound as claimed in any one of the preceding claims, wherein, when one of R^2 to R^5 represents $-\text{D-E}$, then R^2 represents chloro or H.
30. A compound as claimed in any one of the preceding claims, wherein R^2 and/or R^5 independently represent H.

31. A compound as claimed in any one of the preceding claims, wherein R⁶ represents H.
32. A compound as defined in any one of Claims 1 to 31, but without provisos
5 (b) and (d), or a pharmaceutically-acceptable salt thereof, for use as a pharmaceutical.
33. A pharmaceutical formulation including a compound as defined in any one
of Claims 1 to 31, but without provisos (b) and (d), or a pharmaceutically-
10 acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.
34. The use of a compound as defined in any one of Claims 1 to 31, but
without the provisos, or a pharmaceutically-acceptable salt thereof, for the
15 manufacture of a medicament for the treatment of a disease in which inhibition of the activity of a member of the MAPEG family is desired and/or required.
35. A use as claimed in Claim 34, wherein the member of the MAPEG family
is microsomal prostaglandin E synthase-1, leukotriene C₄ and/or 5-lipoxygenase-
20 activating protein.
36. A use as claimed in Claim 35, wherein the member of the MAPEG family is
microsomal prostaglandin E synthase-1.
- 25 37. A use as claimed in any one of Claims 34 to 36, wherein the disease is inflammation.
38. A use as claimed in any one of Claims 34 to 37 wherein the disease is
asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory
30 bowel disease, irritable bowel syndrome, inflammatory pain, fever, 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, hyperprostaglandin E syndrome, classic Bartter syndrome, atherosclerosis, gout, arthritis, osteoarthritis, juvenile arthritis, rheumatoid arthritis, rheumatic fever, ankylosing spondylitis, Hodgkin's disease, 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, an allergic disorder, rhinitis, an ulcer, coronary heart disease, sarcoidosis, any other disease with an inflammatory component, osteoporosis, osteoarthritis, Paget's disease or a periodontal disease.

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39. A method of treatment of a disease in which inhibition of the activity of a member of the MAPEG family 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 31, but without the provisos, or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

40. A method as claimed in Claim 39, wherein the member of the MAPEG family is microsomal prostaglandin E synthase-1, leukotriene C₄ and/or 5-lipoxygenase-activating protein.

20

41. A method as claimed in Claim 40, wherein the member of the MAPEG family is microsomal prostaglandin E synthase-1.

25

42. A combination product comprising:
(A) a compound as defined in any one of Claims 1 to 31, but without the provisos, 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

43. A combination product as claimed in Claim 42 which comprises a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 31, but without the provisos, or a pharmaceutically-acceptable salt thereof, another therapeutic agent that is useful in the treatment of inflammation,
 5 and a pharmaceutically-acceptable adjuvant, diluent or carrier.

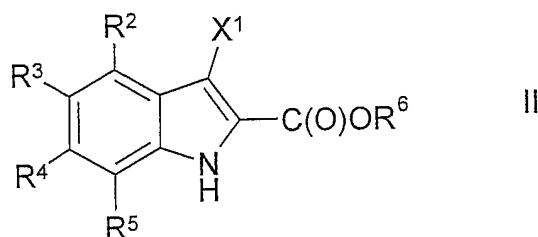
44. A combination product as claimed in Claim 42 which comprises a kit of parts comprising components:

- (a) a pharmaceutical formulation including a compound as defined in any one
 10 of Claims 1 to 31, but without the provisos, 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
 15 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.

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

(i) reaction of a compound of formula II,



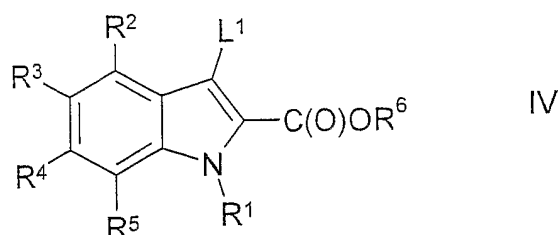
wherein X^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined in Claim 1, with a compound of formula III,



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

(ii) for compounds of formula I in which X^1 represents $-Q-X^2$, in which Q is a single bond or $-C(O)-$, reaction of a compound of formula IV,

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



- 5 wherein Q^a represents a single bond or $-C(O)-$, L^2 represents a suitable leaving group and X^2 is as defined in Claim 1;

(iii) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-C(O)-$, reaction of a compound of formula I in which X^1 represents H with a compound of formula V in which Q^a represents $-C(O)-$;

- 10 (iv) for compounds of formula I in which X^1 represents $-N(R^9)-J-R^{10}$ or $-Q-X^2$ in which Q represents $-O-$ or $-S-$, reaction of a compound of formula IV as defined above with a compound of formula VI,



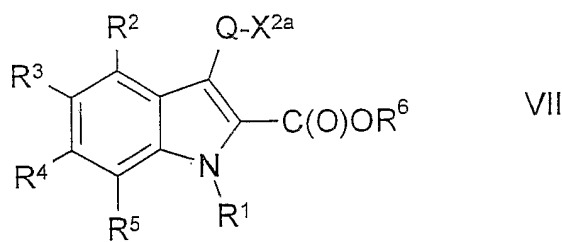
in which X^{1b} represents $-N(R^9)-J-R^{10}$ or $-Q-X^2$ in which Q represents $-O-$ or $-S-$ and R^9 , J , R^{10} and X^2 are as defined in Claim 1;

- 15 (v) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-S-$, reaction of a compound of formula I in which X^1 represents H, with a compound of formula VI in which X^{1b} represents $-Q-X^2$, Q represents $-S-$ and X^2 is as defined in Claim 1;

- 20 (vi) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-S(O)-$ or $-S(O)_2-$, oxidation of a corresponding compound of formula I in which Q represents $-S-$;

- (vii) for compounds of formula I in which X^1 represents $-Q-X^2$, X^2 represents C_{1-8} alkyl substituted by G^1 , G^1 represents $-A^1-R^{11a}$, A^1 represents $-N(R^{12a})A^4-$ and A^4 is a single bond (provided that Q represents a single bond when X^2 represents substituted C_1 alkyl), reaction of a compound of formula VII,
- 25

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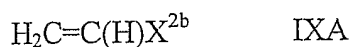
wherein X^{2a} represents a C_{1-8} alkyl group substituted by a $-Z^1$ group in which Z^1 represents $=O$, Q is as defined in Claim 1, provided that it represents a single bond when X^{2a} represents C_1 alkyl substituted by $=O$, and R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as defined in Claim 1 under reductive amination conditions in the presence of a compound of formula VIII,



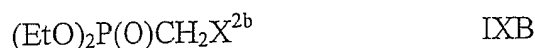
wherein R^{11a} and R^{12a} are as defined in Claim 1;

(viiia) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond, X^2 represents methyl substituted by G^1 , G^1 represents $-A^1-R^{11a}$, A^1 represents $-N(R^{12a})A^4-$ and A^4 is a single bond, reaction of a corresponding compound of formula I in which X^1 represents H , with a mixture of formaldehyde and a compound of formula VIII as defined above;

(viii) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents optionally substituted C_{2-8} alkenyl (in which a point of unsaturation is between the carbon atoms that are α and β to the indole ring), reaction of a corresponding compound of formula IV in which L^1 represents halo with a compound of formula IXA,



or reaction of a compound of formula VII in which Q represents a single bond and X^{2a} represents $-CHO$ with either a compound of formula IXB,



or the like, or a compound of formula IXC,

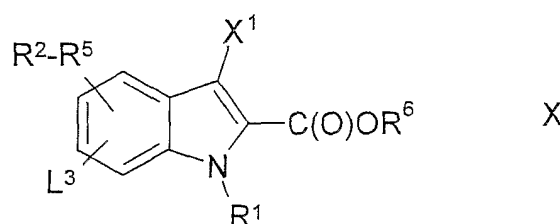


or the like, wherein, in each case, X^{2b} represents H , G^1 or C_{1-6} alkyl optionally substituted with one of more substituents selected from G^1 and/or Z^1 and G^1 and Z^1 are as defined in Claim 1;

(ix) for compounds of formula I in which X^1 represents $-Q-X^2$ and X^2 represents optionally substituted, saturated C_{2-8} alkyl, saturated cycloalkyl, saturated

heterocycloalkyl, C₂₋₈ alkenyl, cycloalkenyl or heterocycloalkenyl, reduction of a corresponding compound of formula I in which X² represents optionally substituted C₂₋₈ alkenyl, cycloalkenyl, heterocycloalkenyl, C₂₋₈ alkynyl, cycloalkynyl or heterocycloalkynyl (as appropriate);

- 5 (x) for compounds of formula I in which one or more of R², R³, R⁴ and/or R⁵ represents -D-E, in which D represents -C(O)-, -C(R⁷)(R⁸)-, C₂₋₄ alkylene or -S(O)₂-, or optionally substituted cycloalkyl or heterocycloalkyl, reaction of a compound of formula X,



- 10 wherein L³ represents L¹ or L² as defined above, which group is attached to one or more of the carbon atoms of the benzenoid ring of the indole, R²-R⁵ represents whichever of the three other substituents on the benzenoid ring are already present in that ring, and X¹, R¹, R², R³, R⁴, R⁵ and R⁶ are as defined in Claim 1, with, in the case where one or more of R² to R⁵ represents -D-E, in which D represents
- 15 -C(O)-, -C(R⁷)(R⁸)-, C₂₋₄ alkylene or -S(O)₂-, a compound of formula XI,



- wherein D^a represents -C(O)-, -C(R⁷)(R⁸)-, C₂₋₄ alkylene or -S(O)₂-, L⁴ represents L¹ (when L³ is L²) or L² (when L³ is L¹), E, R⁷ and R⁸ are as defined in Claim 1 and L¹ and L² are as defined above or, in the case where one of R² to R⁵ represents
- 20 an optionally substituted cycloalkyl or heterocycloalkyl group, a compound of formula XIA,



- wherein (R²⁻⁵) represents whichever one of the substituents R², R³, R⁴ or R⁵ is being introduced and R², R³, R⁴ and R⁵ are as defined in Claim 1 and L⁴ is as
- 25 defined above;

(xi) for compounds of formula I in which when one of R² to R⁵ represents -D-E- and D represents -S-, -O- or C₂₋₄ alkynylene in which the triple bond is adjacent to E, reaction of a compound of formula X as defined above in which L³ represents L² as defined above with a compound of formula XII,

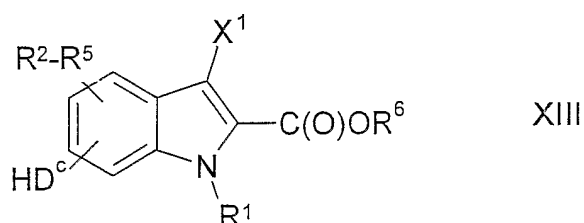
E-D^b-H

XII

wherein D^b represents -S-, -O- or C₂₋₄ alkynylene in which the triple bond is adjacent to E and E is as defined in Claim 1;

- (xii) for compounds of formula I in which when one of R² to R⁵ represents -D-E- and D represents -S(O)- or -S(O)₂-, oxidation of a corresponding compound of formula I in which D represents -S-;

(xiii) for compounds of formula I in which when one of R² to R⁵ represents -D-E- and D represents -O- or -S-, reaction of a compound of formula XIII,

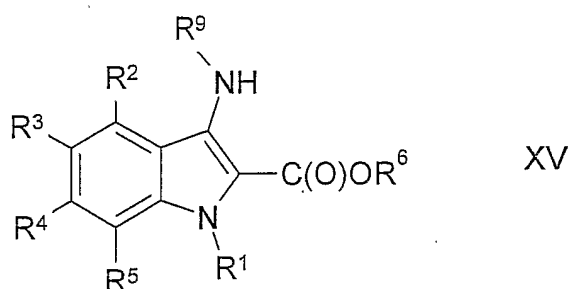


- 10 wherein the -D^c-H group is attached to one or more of the carbon atoms of the benzenoid ring of the indole, D^c represents -O- or -S- and X¹, R¹ and R⁶ are as defined in Claim 1, and R²-R⁵ is as defined above, with a compound of formula XIV,

E-L²

XIV

- 15 wherein L² is as defined above and E is as defined in Claim 1;
- (xiv) for compounds of formula I in which X¹ represents -N(R⁹)-J-R¹⁰, reaction of a compound of formula XV,



- 20 wherein R¹, R², R³, R⁴, R⁵, R⁶ and R⁹ are as defined in Claim 1, with a compound of formula XVI,

R¹⁰-J-L¹

XVI

wherein J and R¹⁰ are as defined in Claim 1 and L¹ is as defined above;

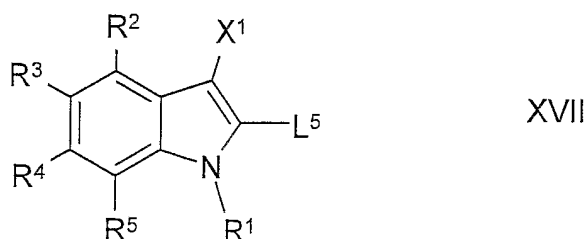
(xv) for compounds of formula I in which X¹ represents -N(R⁹)-J-R¹⁰, J represents a single bond and R¹⁰ represents a C₁₋₈ alkyl group, reduction of a corresponding

compound of formula I, in which J represents $-C(O)-$ and R^{10} represents H or a C_{1-7} alkyl group, in the presence of a suitable reducing agent;

(xvi) for compounds of formula I in which X^1 represents halo, reaction of a compound of formula I wherein X^1 represents H, with a reagent or mixture of

5 reagents known to be a source of halide atoms;

(xvii) for compounds of formula I in which R^6 is other than H, reaction of a compound of formula XVII,



wherein L^5 represents an appropriate alkali metal group, a $-Mg$ -halide, a zinc-based group or a suitable leaving group and X^1 , R^1 , R^2 , R^3 , R^4 and R^5 are as defined in Claim 1, with a compound of formula XVIII,



wherein R^{6a} represents R^6 provided that it does not represent H, and L^6 represents a suitable leaving group;

15 (xviii) for compounds of formula I in which R^6 is H, reaction of a compound of formula XVII in which L^5 represents either:

(I) an alkali metal; or

(II) $-Mg$ -halide,

with carbon dioxide, followed by acidification;

20 (xix) reaction of a compound of formula XVII in which L^5 is a suitable leaving group with CO (or a reagent that is a suitable source of CO), in the presence of a compound of formula XIX,



wherein R^6 is as defined in Claim 1, and an appropriate catalyst system;

25 (xx) for compounds of formula I in which R^6 represents H, hydrolysis of a corresponding compound of formula I in which R^6 does not represent H;

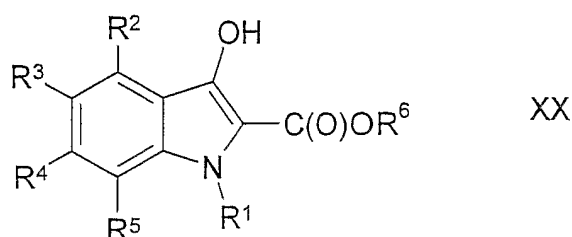
(xxi) for compounds of formula I in which R^6 does not represent H:

(A) esterification of a corresponding compound of formula I in which R^6 represents H; or

(B) trans-esterification of a corresponding compound of formula I in which R^6 does not represent H (and does not represent the same value of R^6 as the compound of formula I to be prepared),

in the presence of the appropriate alcohol of formula XIX as defined above but in which R^6 represents R^{6a} ;

(xxii) for compounds of formula I in which X^1 represents $-Q-X^2$ in which Q represents $-O-$, reaction of a compound of formula XX,



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



wherein L^7 represents a suitable leaving group and X^2 is as defined in Claim 1;

(xxiii) for compounds of formula I in which X^1 represents $-N(R^9)-J-R^{10}$, reaction of a compound of formula XX as defined above, with a compound of formula VI in which X^{1b} represents $-N(R^9)-J-R^{10}$ and R^9 , R^{10} and J are as defined in Claim 1;

(xxiv) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl substituted α to the indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, reaction of a corresponding compound of formula I in which X^1 represents H with a compound corresponding to a compound of formula VI, but in which X^{1b} represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which groups are substituted by a Z^1 group in which Z^1 represents $=O$;

(xxv) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{2-8} alkyl substituted by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H, reaction of a corresponding compound of formula I in which X^2 represents C_{1-7} alkyl substituted by a Z^1 group in which Z^1 represents $=O$, with the corresponding Grignard reagent derivative of a compound of formula V in which

L^2 represents chloro, bromo or iodo, Q^a is a single bond and X^2 represents C_{1-7} alkyl;

(xxvi) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond, and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which are unsubstituted in the position α to the indole ring, reduction of a corresponding compound of formula I in which X^2 represents C_{1-8} alkyl substituted α to the indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{11a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{11a} represents H;

(xxvii) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond and X^2 represents C_{1-8} alkyl or heterocycloalkyl, neither of which are substituted by Z^1 in which Z^1 represents $=O$, reduction of a corresponding compound of formula I in which X^2 represents C_{1-8} alkyl or heterocycloalkyl, which groups are substituted by one or more Z^1 groups in which Z^1 represents $=O$;
or

(xxviii) for compounds of formula I in which one of the groups R^2 , R^3 , R^4 or R^5 represents a heterocycloalkyl group linked to the benzenoid moiety of the indole ring by a nitrogen atom, reaction of a compound of formula X as defined above with a compound of formula XXIA,



wherein (R^{2y-5y}) represents R^{2-5} as defined above provided that the appropriate R^2 , R^3 , R^4 or R^5 substituent represents a heterocycloalkyl group in which the hydrogen atom of the compound of formula XXIA is attached to a nitrogen atom of that group.

INTERNATIONAL SEARCH REPORT

Inte application No
PCT/GB2005/004978

A. CLASSIFICATION OF SUBJECT MATTER

C07D209/42 C07D401/04 A61K31/404 A61P11/00 A61P29/00
C07D405/12 C07D401/12 C07D401/14

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/43672 A (GENETICS INSTITUTE, INC) 2 September 1999 (1999-09-02) cited in the application the whole document	1,33-44
A	US 5 374 615 A (POSS ET AL) 20 December 1994 (1994-12-20) cited in the application the whole document	1



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"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

20 March 2006

Date of mailing of the international search report

05/04/2006

Name and mailing address of the ISA/

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Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2005/004978

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 39-41 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

International application No
PCT/GB2005/004978

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