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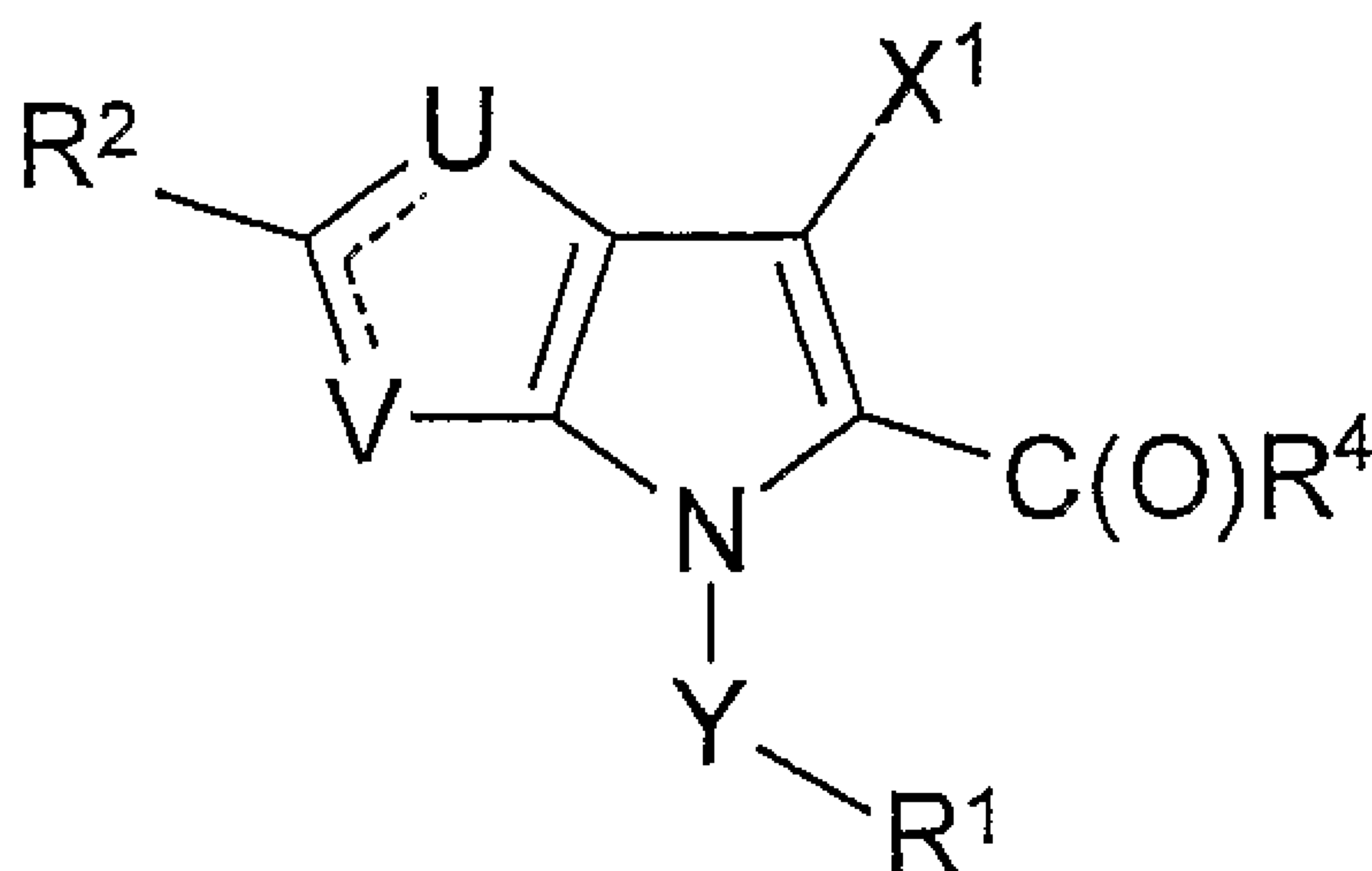
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(54) Titre : THIENOPYRROLES UTILES DANS LE TRAITEMENT DE L'INFLAMMATION
(54) Title: THIENOPYRROLES USEFUL IN THE TREATMENT OF INFLAMMATION



(I)

(57) Abrégé/Abstract:

There is provided compounds of formula I: wherein the dotted lines, U5 V5 X¹, Y, R¹, R² and R⁴ 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.

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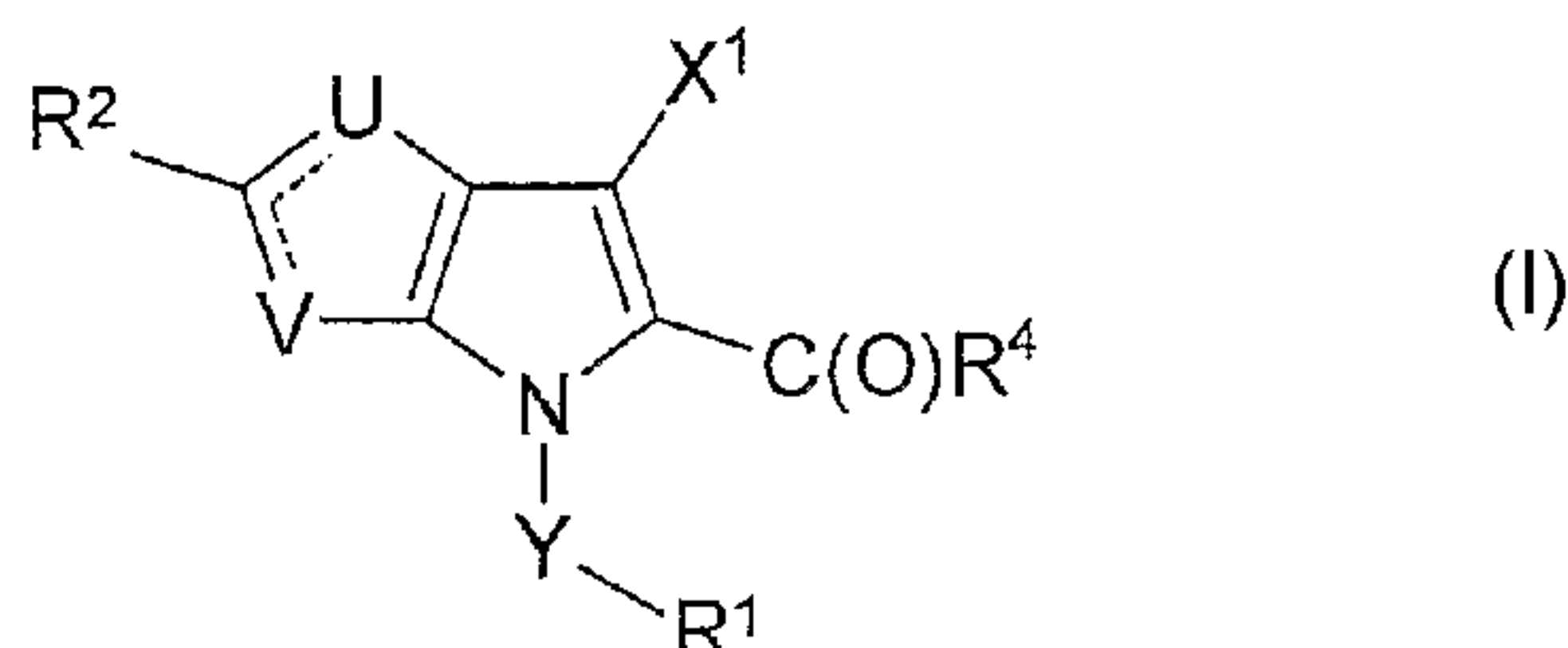
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(54) Title: THIENOPYRROLES USEFUL IN THE TREATMENT OF INFLAMMATION



(57) Abstract: There is provided compounds of formula I: wherein the dotted lines, U5 V5 X¹, Y, R¹, R² and R⁴ 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.

THIENOPYRROLES 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 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 conditions is a lack of efficacy and/or the prevalence of side effects (real or perceived).

20

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

25

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 inflammatory components adding to the symptomatology of the patients.

30

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.

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

10 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.

15 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.

25 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
5 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
10 (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
15 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
20 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.

25 **Prior Art**

Indole-2-carboxylates, and derivatives thereof, are disclosed in international patent applications WO 2005/005415, WO 2005/123675, WO 2005/123673 and WO
2005/123674 for use as inhibitors of mPGES and thus in the treatment of
30 inflammation. Thienopyrroles are neither mentioned nor suggested in any of these documents.

International patent application WO 2004/022537 discloses thienopyrrol-5-yl-(4-methylpiperazinyl-1-yl)methanone derivatives for use in the treatment of diseases mediated by the histamine H₄ receptor. However, this document does not disclose compounds with aromatic substituents attached to the ring system *via* the pyrrole
5 nitrogen.

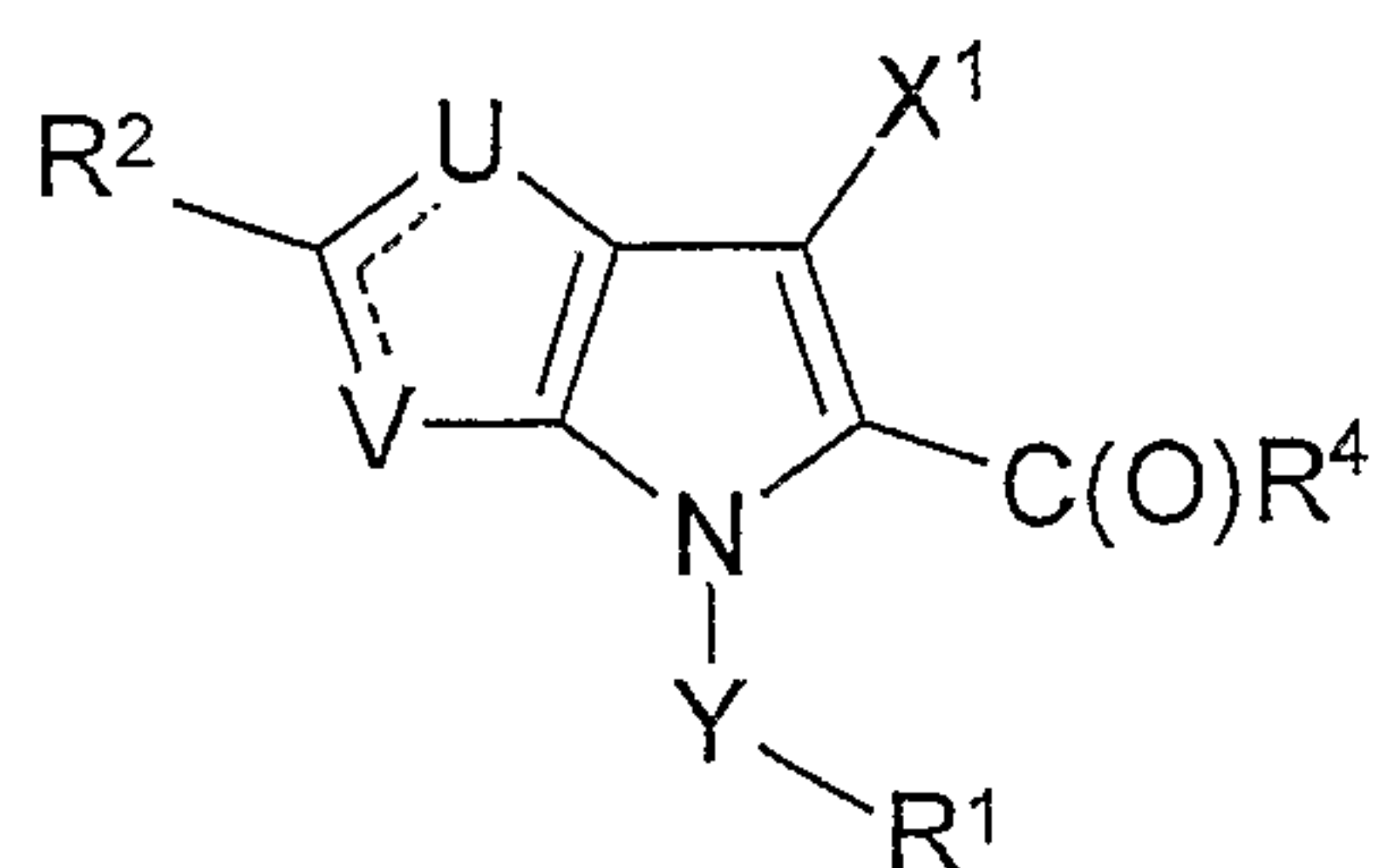
Certain thieno[2,3-b]pyrrol-5-yl carboxylic esters have been disclosed by Sommen *et al* in *Tetrahedron*, **59**, 1557 (2003) and *Synlett*, 1731 (2001), by El-Hamed *et al* in *Bulletin of the Faculty of Pharmacy (Cairo University)*, **39**, 11 (2001), and by
10 El-Shafei *et al* in *Phosphorus, Sulfur and Silicon and the Related Elements*, **73**, 15 (2001), as chemical curiosities. The use of these compounds in the treatment of inflammation is neither mentioned nor suggested in any of these documents.

Kumar *et al* recently disclosed certain thieno[3,2-b]pyrrol-5-yl carboxylic esters as
15 antiinflammatory agents in *Bioorg. Med. Chem.*, **12**, 1221 (2004). However, compounds that are substituted with an aryl group, or a heteroaryl group, attached either directly or *via* a linker at the 4(*N*)-position and/or substituted with either an aryl group, a heteroaryl group or heterocycloalkyl group at the 2-position, i.e. on the thiophene ring are neither mentioned nor suggested in these documents.

20 Finally, international patent application WO 99/40914 discloses 4(*N*)-benzylthienopyrrol-5-yl carboxylic acids and esters for use as inhibitors of monocyte chemoattractant protein-1 (MCP-1).

25 Disclosure of the Invention

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



I

wherein

5 one of U and V represents -S- and the other represents -C(R³)-;

when U represents -S-, the dotted line between the carbon atom bearing R² and V is a double bond and that between the carbon atom bearing R² and U is a single bond, and when V represents -S-, the dotted line between the carbon atom bearing
 10 R² and U is a double bond and that between the carbon atom bearing R² and V is a single bond;

one of the groups R² and R³ represents -D-E and the other represents H, halo, -NO₂, cyano or C₁₋₆ alkyl, which alkyl group is optionally substituted by one or
 15 more substituents selected from halo, hydroxy and C₁₋₆ alkoxy;

D represents a single bond, -O-, -C(R⁶)(R⁷)-, C₂₋₄ alkylene, -C(O)- or -S(O)_m-;

R¹ represents an aryl group or a heteroaryl group, both of which groups are
 20 optionally substituted by one or more substituents selected from A;

E represents either an aryl or heteroaryl group (both of which groups are optionally substituted by one or more substituents selected from A), or a heterocycloalkyl group (which group is optionally substituted by one or more
 25 substituents selected from G¹ and/or Z¹);

R⁶ and R⁷ independently represent H, halo or C₁₋₆ alkyl, which latter group is optionally substituted by halo, or R⁶ and R⁷ 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 C₁₋₃ alkyl, which latter group is optionally substituted by one or more halo substituents;

5

X¹ represents H, halo, -N(R⁸)-J-R⁹ or -Q-X²;

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

10

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

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

X² represents:

15

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

(b) C₁₋₈ alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G¹ and/or Z¹;

20

Y represents a single bond, or a C₁₋₈ alkylene or C₂₋₈ heteroalkylene chain, both of which latter two groups:

(i) optionally contain one or more unsaturations (for example double or triple bonds);

25

(ii) are optionally substituted by one or more substituents selected from halo, -R^{10a}, -N(R^{10b})R^{11b}, -OR^{10c} and =O; and/or

30

(iii) may comprise an additional 3- to 8-membered ring formed between any one or more (e.g. one or two) members of the C₁₋₈ alkylene or C₂₋₈ heteroalkylene chain, which ring optionally contains 1 to 3 heteroatoms and/or 1 to 3 unsaturations (for example double or triple bonds) and which ring is itself optionally substituted by one or more substituents selected from halo, -R^{10d}, -N(R^{10e})R^{11e}, -OR^{10f} and =O;

R^4 represents $-OR^{12a}$ or $-N(R^{12b})R^{13b}$;

R^8, R^9, R^{10a} to $R^{10f}, R^{11b}, R^{11e}, R^{12a}, R^{12b}$ and R^{13b} independently represent, on each occasion when mentioned above:

- I) hydrogen;
- II) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from B;
- 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^8 and R^9, R^{10b} and R^{11b}, R^{10e} and R^{11e} , and R^{12b} and R^{13b} (as appropriate), may be linked together to form, along with the N atom and (in the case of R^9) the J group to which they are 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 ;

15

A represents, on each occasion when mentioned above:

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

G^1 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^{14a}$;

25 wherein A^1 represents a single bond or a spacer group selected from $-C(O)A^2-$, $-S(O)_2A^3-$, $-N(R^{15a})A^4-$ or $-OA^5-$, in which:

A^2 represents a single bond, $-O-$, $-N(R^{15b})-$ or $-C(O)-$;

A^3 represents a single bond, $-O-$ or $-N(R^{15c})-$;

A^4 and A^5 independently represent a single bond, $-C(O)-$, $-C(O)N(R^{15d})-$,

30 $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{15e})-$;

Z^1 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{14b}$, $=NS(O)_2N(R^{15f})R^{14c}$, $=NCN$ or $=C(H)NO_2$;

B represents, on each occasion when mentioned above:

- 5 I) an aryl group or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from G^2 ;
- 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;

10

G^2 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^6-R^{16a}$;

wherein A^6 represents a single bond or a spacer group selected from $-C(O)A^7-$, $-S(O)_2A^8-$, $-N(R^{17a})A^9-$ or $-OA^{10}-$, in which:

15 A^7 represents a single bond, $-O-$, $-N(R^{17b})-$ or $-C(O)-$;

A^8 represents a single bond, $-O-$ or $-N(R^{17c})-$;

A^9 and A^{10} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{17d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{17e})-$;

20 Z^2 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{16b}$, $=NS(O)_2N(R^{17f})R^{16c}$, $=NCN$ or $=C(H)NO_2$;

R^{14a} , R^{14b} , R^{14c} , R^{15a} , R^{15b} , R^{15c} , R^{15d} , R^{15e} , R^{15f} , R^{16a} , R^{16b} , R^{16c} , R^{17a} , R^{17b} , R^{17c} , R^{17d} , R^{17e} and R^{17f} are independently selected from:

- 25 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 one or more substituents selected from G^3 and/or Z^3 ; or
- 30 any pair of R^{14a} to R^{14c} and R^{15a} to R^{15f} , and/or R^{16a} to R^{16c} and R^{17a} to R^{17f} , may, for example when present on the same or on adjacent atoms, be linked together to form with those, or other relevant, atoms a further 3- to 8-membered ring,

optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from G^3 and/or Z^3 ;

G^3 represents, on each occasion when mentioned above, halo, cyano, $-N_3$, $-NO_2$,
5 $-ONO_2$ or $-A^{11}-R^{18a}$;

wherein A^{11} represents a single bond or a spacer group selected from $-C(O)A^{12}-$,
 $-S(O)_2A^{13}-$, $-N(R^{19a})A^{14}-$ or $-OA^{15}-$, in which:

A^{12} represents a single bond, $-O-$, $-N(R^{19b})-$ or $-C(O)-$;

A^{13} represents a single bond, $-O-$ or $-N(R^{19c})-$;

10 A^{14} and A^{15} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{19d})-$,
 $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{19e})-$;

Z^3 represents, on each occasion when mentioned above, $=O$, $=S$, $=NOR^{18b}$,
15 $=NS(O)_2N(R^{19f})R^{18c}$, $=NCN$ or $=C(H)NO_2$;

R^{18a} , R^{18b} , R^{18c} , R^{19a} , R^{19b} , R^{19c} , R^{19d} , R^{19e} and R^{19f} are independently selected from:

i) hydrogen;

ii) C_{1-6} alkyl or a heterocycloalkyl group, both of which groups are optionally
20 substituted by one or more substituents selected from halo, C_{1-4} alkyl,
 $-N(R^{20a})R^{21a}$, $-OR^{20b}$ and $=O$; and

iii) an aryl or heteroaryl group, both of which are optionally substituted by one
or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{20c})R^{21b}$ and $-OR^{20d}$; or
any pair of R^{18a} to R^{18c} and R^{19a} to R^{19f} may, for example when present on the
25 same or on adjacent atoms, be linked together to form with those, or other
relevant, atoms a further 3- to 8-membered ring, optionally containing 1 to 3
heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by
one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{20e})R^{21c}$, $-OR^{20f}$ and
 $=O$;

R^{20a} , R^{20b} , R^{20c} , R^{20d} , R^{20e} , R^{20f} , R^{21a} , R^{21b} and R^{21c} 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^2 represents -D-E and:

(a) V represents S, D represents -C(O)-, E represents phenyl, X^1 represents -Q- X^2 , Q represents a single bond, R^3 and X^2 both represent methyl, R^4 represents
10 ethoxy and Y represents a single bond, then R^1 does not represent an unsubstituted phenyl group; and

(b) when U represents S, D represents a single bond, E represents thien-2-yl or 3-aminophenyl, X^1 and R^3 both represent H, R^4 represents -OH or ethoxy and Y represents -CH₂-, then R^1 does not represent 3,4-dichlorophenyl,
15

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

Pharmaceutically-acceptable salts include acid addition salts and base addition
20 salts. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of a compound of formula I with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using standard techniques (e.g. *in vacuo*, by freeze-drying or by
25 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*
30 (*entgegen*) and *Z* (*zusammen*) geometric isomers about each individual double bond. All such isomers and mixtures thereof are included within the scope of the invention.

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

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

Unless otherwise specified, C_{1-q} alkyl, the alkyl part of C_{1-q} alkoxy, and C_{1-q} alkylene, groups (where q is the upper limit of the range) defined herein may be
25 straight-chain or, when there is a sufficient number (i.e. a minimum of two or three, as appropriate) of carbon atoms, be branched-chain, and/or cyclic (so forming, in the case of alkyl, 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
30 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).

C_{3-q} cycloalkyl groups (where q is the upper limit of the range) that may be mentioned may be monocyclic or bicyclic alkyl groups, which cycloalkyl groups may further be bridged (so forming, for example, fused ring systems such as three
5 fused cycloalkyl groups). Such cycloalkyl groups may be saturated or unsaturated containing one or more double or triple bonds (forming for example a C_{3-q} cycloalkenyl or a C_{8-q} cycloalkynyl group). 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
10 atom on the cycloalkyl group, forming a so-called "spiro"-compound.

C₂₋₈ heteroalkylene chains include C₂₋₈ alkylene chains that are interrupted by one or more heteroatom groups selected from -O-, -S- or -N(R²⁴)-, in which R²⁴ represents C₁₋₄ alkyl, optionally substituted by one or more halo (e.g. fluoro)
15 groups.

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

Heterocycloalkyl groups that may be mentioned include non-aromatic monocyclic
20 and bicyclic groups 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
25 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_{8-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,
30 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]heptany, 6-oxabicyclo-
[3.2.1]octany, oxetany, oxirany, piperaziny, piperidiny, pyran, pyrazolidiny,
pyrrolidinony, pyrrolidiny, pyrroliny, quinuclidiny, sulfolany, 3-sulfoleny,
5 tetrahydropyran, tetrahydrofuran, tetrahydropyridyl (such as 1,2,3,4-
tetrahydropyridyl and 1,2,3,6-tetrahydropyridyl), thietany, thiirany, thiolany,
thiomorpholiny, trithianyl (including 1,3,5-trithianyl), tropany 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
10 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*-
15 oxidised form.

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

Aryl groups that may be mentioned include C₆₋₁₄ (such as C₆₋₁₃ (e.g. C₆₋₁₀)) aryl
25 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
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
30 are linked to the rest of the molecule *via* an aromatic ring.

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).

5 Heterocyclic groups that may be mentioned include benzothiadiazolyl (including 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-
10 benzoxazinyl), benzoxazolyl, benzomorpholinyl, benzoselenadiazolyl (including 2,1,3-benzoselenadiazolyl), benzothienyl, carbazolyl, chromanyl, cinnolinyl, furanyl, imidazolyl, imidazo[1,2-*a*]pyridyl, indazolyl, indolinyl, indolyl, isobenzofuranyl, isochromanyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, naphthyridinyl (including 1,6-naphthyridinyl or, preferably, 1,5-naphthyridinyl and 1,8-naphthyridinyl), oxadiazolyl (including
15 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl and 1,3,4-oxadiazolyl), oxazolyl, phenazinyl, phenothiazinyl, phthalazinyl, pteridinyl, purinyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinolizinyl, quinoxalinyl, tetrahydroisoquinolinyl (including 1,2,3,4-tetrahydroisoquinolinyl
20 and 5,6,7,8-tetrahydroisoquinolinyl), tetrahydroquinolinyl (including 1,2,3,4-tetrahydroquinolinyl and 5,6,7,8-tetrahydroquinolinyl), tetrazolyl, thiadiazolyl (including 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl and 1,3,4-thiadiazolyl), thiazolyl, thiochromanyl, thienyl, triazolyl (including 1,2,3-triazolyl, 1,2,4-triazolyl and 1,3,4-triazolyl) and the like. Substituents on heteroaryl groups may, where
25 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.

30

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

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
5 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
10 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.

For the avoidance of doubt, when a term such as " R^{10a} to R^{10c} " is employed herein,
15 this will be understood by the skilled person to mean R^{10a} , R^{10b} and R^{10c} inclusively.

Compounds of the invention that may be mentioned include those in which when E represents an optionally substituted heterocycloalkyl group, it is a C_{4-5}
20 heterocycloalkyl group (which group is preferably a nitrogen-containing heterocycloalkyl group, optionally containing a further nitrogen and/or oxygen atom) optionally substituted by one or more (e.g. one) substituents selected from G^1 and/or, preferably, Z^1 .

25 Further compounds of the invention that may be mentioned include those in which when E represents an optionally substituted heterocycloalkyl group, then D represents C_{1-3} alkylene or, preferably, a single bond.

Yet further compounds of the invention that may be mentioned include those in
30 which E represents an aryl or a heteroaryl group, both of which are optionally substituted by one or more substituents selected from A.

Preferred compounds of the invention include those in which:

A represents G^1 ; an aryl group or a heteroaryl group, both of which are optionally substituted by one or more B groups; a C_{1-5} alkyl group, which alkyl group is optionally unsaturated and is optionally substituted by one or more G^1 groups;

5 X^2 represents optionally substituted aryl or heteroaryl, C_{1-6} alkyl or heterocycloalkyl (which latter two groups are preferably substituted with one or more (e.g. one) groups selected from G^1 and/or Z^1);

R^8 represents H or C_{1-2} alkyl (e.g. methyl);

10 R^9 represents C_{1-6} (e.g. C_{1-3}) alkyl, which group may be unsubstituted, but is preferably substituted by one or more (e.g. one) groups selected from G^1 ;

or R^8 and R^9 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 and J group to which R^8 and R^9 are respectively attached) a further heteroatom (e.g. nitrogen or oxygen) and which ring is optionally substituted by one or more

15 (e.g. two) Z^1 groups;

R^{10a} to R^{10f} , R^{11b} and R^{11e} independently represent H or C_{1-2} alkyl;

G^1 represents halo, $-NO_2$ or $-A^1-R^{14a}$;

A^1 represents $-N(R^{15a})A^4-$ or, preferably, a single bond, $-C(O)A^2-$ or $-OA^5-$;

A^2 represents $-O-$;

20 A^4 and A^5 independently represent a single bond, $-C(O)-$, $-C(O)N(R^{15d})-$ or $-C(O)O-$;

R^{14a} to R^{14c} independently represent hydrogen, an aryl group, a heteroaryl group, C_{1-7} alkyl or a heterocycloalkyl group (such as C_{4-8} heterocycloalkyl, which group contains one nitrogen atom and, optionally, a further nitrogen or oxygen atom),

25 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;

R^{15a} to R^{15f} independently represent C_{1-2} alkyl or, preferably, hydrogen;

or any pair of R^{14a} to R^{14c} and R^{15a} to R^{15f} , together with the atom(s) to which they are attached, represent a nitrogen-containing heterocycloalkyl group optionally

30 substituted by one or more G^3 and/or Z^3 groups;

Z^1 represents $=NOR^{14b}$, $=NCN$ or, preferably, $=O$;

B represents C_{1-3} alkyl or G^2 ;

G^2 represents cyano, $-N_3$, halo, $-NO_2$ or $-A^6-R^{16a}$;

A^6 represents $-N(R^{17a})A^9-$ or $-OA^{10}-$;

A^9 represents $-C(O)N(R^{17d})-$, $-C(O)O-$ or, more preferably, a single bond or $-C(O)-$;

5 A^{10} represents a single bond;

R^{16a} to R^{16c} independently represent C_{1-3} alkyl;

Z^2 represents $=NOR^{16b}$, $=NCN$ or, more preferably, $=O$;

G^3 represents halo or $-A^{11}-R^{18a}$;

A^{11} represents a single bond, $-OA^{15}-$ or, more preferably, $-C(O)A^{12}-$;

10 A^{12} represents $-O-$;

A^{15} represents a single bond,

when any one of R^{18a} , R^{18b} , R^{18c} , R^{19a} , R^{19b} , R^{19c} , R^{19d} , R^{19e} and R^{19f} represents optionally substituted C_{1-6} alkyl, the optional substituent is one or more halo groups;

15 R^{18a} to R^{18c} independently represent C_{1-4} alkyl, aryl or H;

Z^3 represents $=O$;

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

when any one of R^{20a} , R^{20b} , R^{20c} , R^{20d} , R^{20e} , R^{20f} , R^{21a} , R^{21b} and R^{21c} represents optionally substituted C_{1-4} alkyl, the optional substituent is one or more fluoro

20 groups.

Preferred aryl and heteroaryl groups that R^1 , X^2 (when X^2 represents an aryl or heteroaryl group) and/or E may represent include optionally substituted phenyl, naphthyl, pyrrolyl, furanyl, thienyl (e.g. thien-2-yl or thien-3-yl), pyrazolyl, imidazolyl (e.g. 1-imidazolyl, 2-imidazolyl or 4-imidazolyl), oxazolyl, isoxazolyl, 25 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, benzothienyl, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, 30 benzimidazolyl, quinazolinyl, quinoxaliny, 1,3-benzodioxolyl, tetrazolyl, benzothiazolyl, and/or benzodioxanyl, group. Preferred values include phenyl, thienyl, pyridyl and imidazolyl.

Preferred values of E, when R² and/or R³ represent -D-E include optionally substituted pyridyl, phenyl, thienyl (e.g. 2-thienyl) and imidazolyl.

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

More preferred compounds of the invention include those in which:

X¹ represents H, halo (such as iodo, chloro or fluoro) or -Q-X²;

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

X² represents an aryl (e.g. phenyl) group or a heteroaryl group, both of which are optionally substituted with one or more A groups as defined herein, or an optionally unsaturated C₁₋₃ alkyl (e.g. methyl or ethynyl) group optionally substituted with one or more G¹ groups;

- 15 A represents G¹; a phenyl group, a thienyl (such as a thien-2-yl) group, both of which are optionally substituted by one or more B groups; or a methyl, ethyl, ethenyl, ethynyl or *t*-butyl group, each of which is optionally substituted by one or more G¹ groups;

- 20 Y represents a C₁₋₃ alkylene spacer group (such as an ethylene or, preferably, a methylene group) or, more preferably, a single bond;

the R² or R³ group (as appropriate) that does not represent -D-E represents H, halo (such as iodo) or C₁₋₃ alkyl (such as methyl);

D represents -C(R⁶)(R⁷)- or, preferably, a single bond or a C₁₋₃ alkylene (e.g. an ethynylene) linker group;

- 25 R⁶ and R⁷ independently represent H, fluoro or C₁₋₆ (e.g. C₁₋₂) alkyl (such as methyl); or

R⁶ and R⁷ are linked together to form a C₃₋₆ (e.g. C₃₋₄) cycloalkyl group;

R^{12a} and R^{12b} independently represent H or C₁₋₃ alkyl, such as methyl;

when R⁴ represents -N(R^{12b})R^{13b}, R^{12b} represents H and R^{13b} represents a C₁₋₄ alkyl

- 30 group (e.g. an ethyl group) substituted by G¹;

when R⁴ represents -OR^{12a}, R^{12a} represents H;

G¹ represents fluoro, chloro, -NO₂ or -A¹-R^{14a};

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

R^{14a} to R^{14c} independently represent H, an aryl (e.g. phenyl) group, a heteroaryl (such as tetrazolyl (e.g. 5-tetrazolyl), imidazolyl (e.g. 4-imidazolyl or 2-imidazolyl) or, more preferably, pyridyl (e.g. 2-pyridyl, 3-pyridyl or, especially, 4-pyridyl) or thiazolyl (e.g. 5-thiazolyl)) group, a linear C_{1-6} alkyl group (such as a methyl or an ethyl group), an unsaturated C_{2-6} alkyl group (such as an ethenyl or an ethynyl group), a branched C_{2-6} alkyl group (such as an isopropyl group), or a cyclic C_{3-6} alkyl group (such as a cyclopropyl or cyclopentyl group), which latter six groups are optionally substituted with one or more G^3 substituents;

10 B represents methyl or G^2 ;

G^2 represents $-A^6-R^{16a}$;

A^6 represents $-OA^{10}-$;

R^{16a} to R^{16c} independently represent methyl or ethyl;

G^3 represents fluoro or $-A^{11}-R^{18a}$;

15 A^{11} represents $-C(O)O-$;

R^{18a} to R^{18c} independently represent C_{1-3} alkyl (such as a methyl group or an ethyl group), a phenyl group or, more preferably, H.

Optional substituents on R^1 , X^2 (when X^2 represents an aryl or heteroaryl group)

20 and E groups are preferably selected from:

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

cyano;

$-NO_2$;

25 C_{1-6} alkyl, which alkyl group may be linear or branched (e.g. C_{1-4} alkyl (including ethyl, *n*-propyl, isopropyl, *n*-butyl or, preferably, methyl or *t*-butyl), *n*-pentyl, isopentyl, *n*-hexyl or isohexyl), cyclic (e.g. cyclopropyl, cyclobutyl, cyclohexyl or, preferably, cyclopentyl), part-cyclic (e.g. cyclopropylmethyl), unsaturated (e.g. 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 4-pentenyl, 5-hexenyl or, preferably, ethenyl or ethynyl) and/or optionally

30 substituted with one or more $-CO_2H$ groups (so forming e.g. a carboxyvinyl group), one or more halo (e.g. fluoro) group (so forming e.g. a fluoromethyl, a

difluoromethyl or, preferably, a trifluoromethyl group), or one or more phenyl groups (so forming e.g. a phenylethynyl group);

aryl (e.g. phenyl), optionally substituted by one or more halo or, preferably, C₁₋₄ alkoxy (e.g. ethoxy or isopropoxy) group;

5 heteroaryl (e.g. thienyl, such as thien-2-yl), optionally substituted by one or more halo or, preferably, C₁₋₃ alkyl (e.g. methyl) group;

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

10 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; -OR²²; and

-N(R²²)R²³;

15 wherein R²² and R²³ independently represent, on each occasion when mentioned above, H, phenyl or C₁₋₆ alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *t*-butyl or cyclopropyl (which alkyl groups are optionally substituted by one or more -CO₂H groups (so forming e.g. a carboxypropan-2-yl group) or one or more halo (e.g. fluoro) groups (so forming e.g. a trifluoromethyl group)).

20

Particularly preferred values of X² include C₁₋₃ 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.

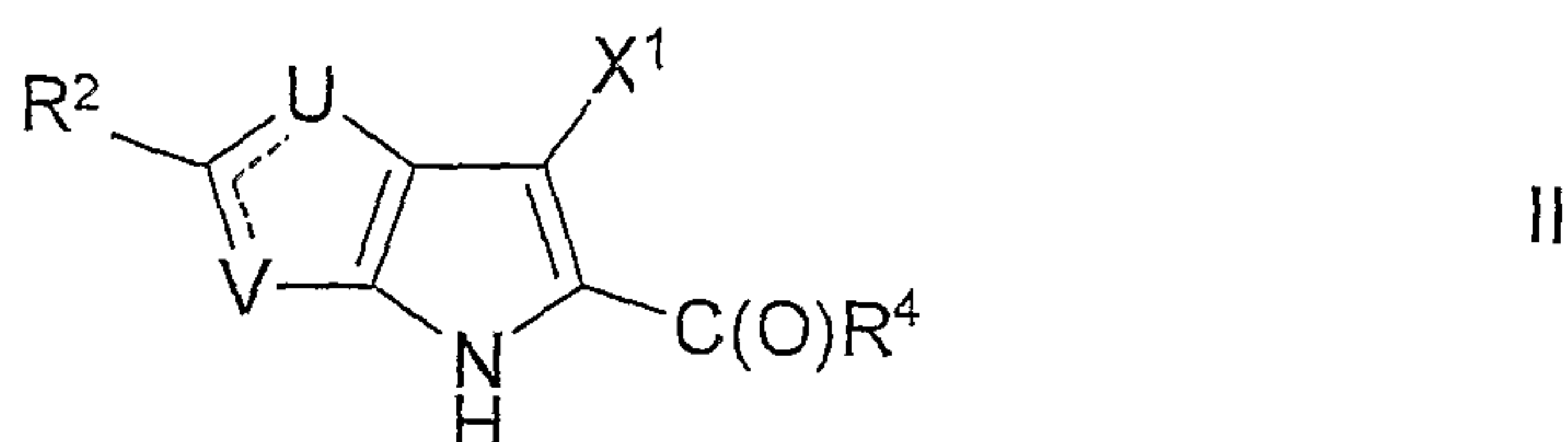
25 Particularly preferred compounds of the invention include those of the examples described hereinafter.

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.

30

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,

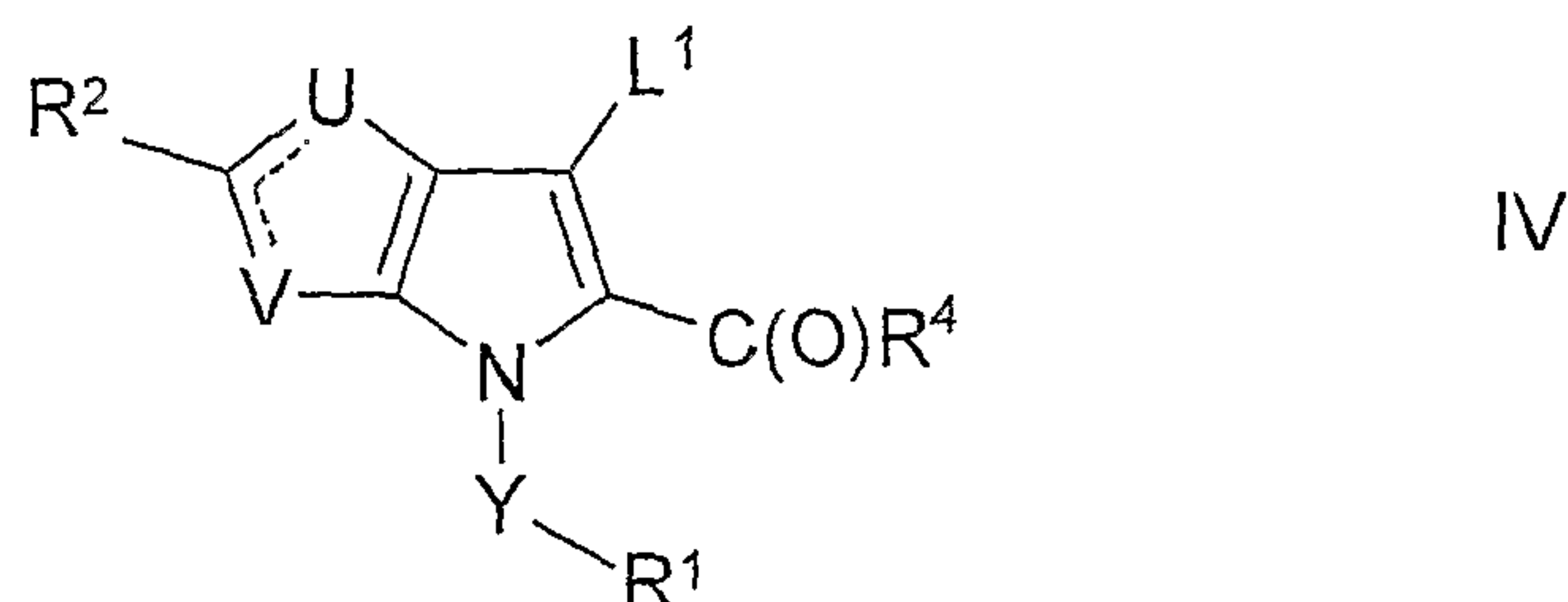


wherein the dotted lines, U, V, X¹, R² and R⁴ are as hereinbefore defined, with a compound of formula III,



wherein L¹ represents a suitable leaving group such as chloro, bromo, iodo, a sulfonate group (e.g. -OS(O)₂CF₃, -OS(O)₂CH₃, -OS(O)₂PhMe or a nonaflate) or -B(OH)₂ and R¹ and Y are 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 PPh₃, 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 X^1 represents $-Q-X^2$, in which Q is a single bond or $-C(O)-$, reaction of a compound of formula IV,



5

wherein the dotted lines, U, V, L^1 , R^1 , R^2 , R^4 and Y are as hereinbefore defined, with a compound of formula V,



10

wherein Q^a represents a single bond or $-C(O)-$, L^2 represents a suitable leaving group such as chloro, bromo, iodo, $-B(OH)_2$ or a protected derivative thereof, for example a 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl group, 9-borabicyclo[3.3.1]nonane (9-BBN), $-Sn(alkyl)_3$ (e.g. $-SnMe_3$ or $-SnBu_3$), or a similar group known to the skilled person, and X^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 $-C(O)-$ include chloro or bromo groups, and preferred leaving groups for compounds of formula V in which Q^a is a single bond include $-B(OH)_2$, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl, 9-borabicyclo[3.3.1]nonane (9-BBN), or $-Sn(alkyl)_3$. 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, Pd/C, $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$ or $NiCl_2$ and a ligand such as *t*-Bu₃P, (C₆H₁₁)₃P, PPh₃, 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'-binaphthyl, 1,1'-bis(diphenylphosphino)ferrocene, 1,3-bis(diphenylphosphino)propane, xantphos, or a mixture thereof, together with 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
5 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 L¹ represents chloro, bromo or iodo) are also compounds of formula I and therefore compounds of the invention. In the case where Q^a
10 represents a single bond and X² represents either C₂₋₈ alkenyl, cycloalkenyl or heterocycloalkenyl in which the double bond is between the carbon atoms that are α and β to L², 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;

15

(iii) for compounds of formula I in which X¹ represents -Q-X² and Q represents -C(O)-, reaction of a compound of formula I in which X¹ represents H with a compound of formula V in which Q^a represents -C(O)- and L² represents a suitable leaving group such as chloro or bromo, -N(C₁₋₆ alkyl)₂ (e.g. -N(CH₃)₂) or
20 a carboxylate group such as -O-C(O)-X^{2y} in which X^{2y} represents X² or H. In the latter case, X^{2y} and X² are preferably the same, or X^{2y} represents e.g. H, CH₃ or CF₃. 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. AlCl₃ or FeCl₃). Reaction of a compound of formula V in which L² represents
25 -N(C₁₋₆ alkyl)₂ and X² represents optionally substituted aryl (e.g. phenyl) or heteroaryl may be performed in the presence of a reagent such as POCl₃, 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, POCl₃ may convert the compound of formula V into one in which L² represents
30 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 X¹ represents H;

(iv) for compounds of formula I in which X^1 represents $-N(R^8)-J-R^9$ 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,

5



in which X^{1b} represents $-N(R^8)-J-R^9$ or $-Q-X^2$ in which Q represents $-O-$ or $-S-$ and R^8 , J, R^9 and X^2 are as hereinbefore defined, for example under reaction conditions as hereinbefore described in respect of either process (i) or (ii) above;

10

(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. 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 ($PhI(OC(O)CF_3)_2$) in a suitable solvent such as $(CF_3)_2CHOH$. Introduction of such an $-S-X^2$ group is described in *inter alia* *Bioorg. Med. Chem. Lett.*, **14**, 4741-4745 (2004);

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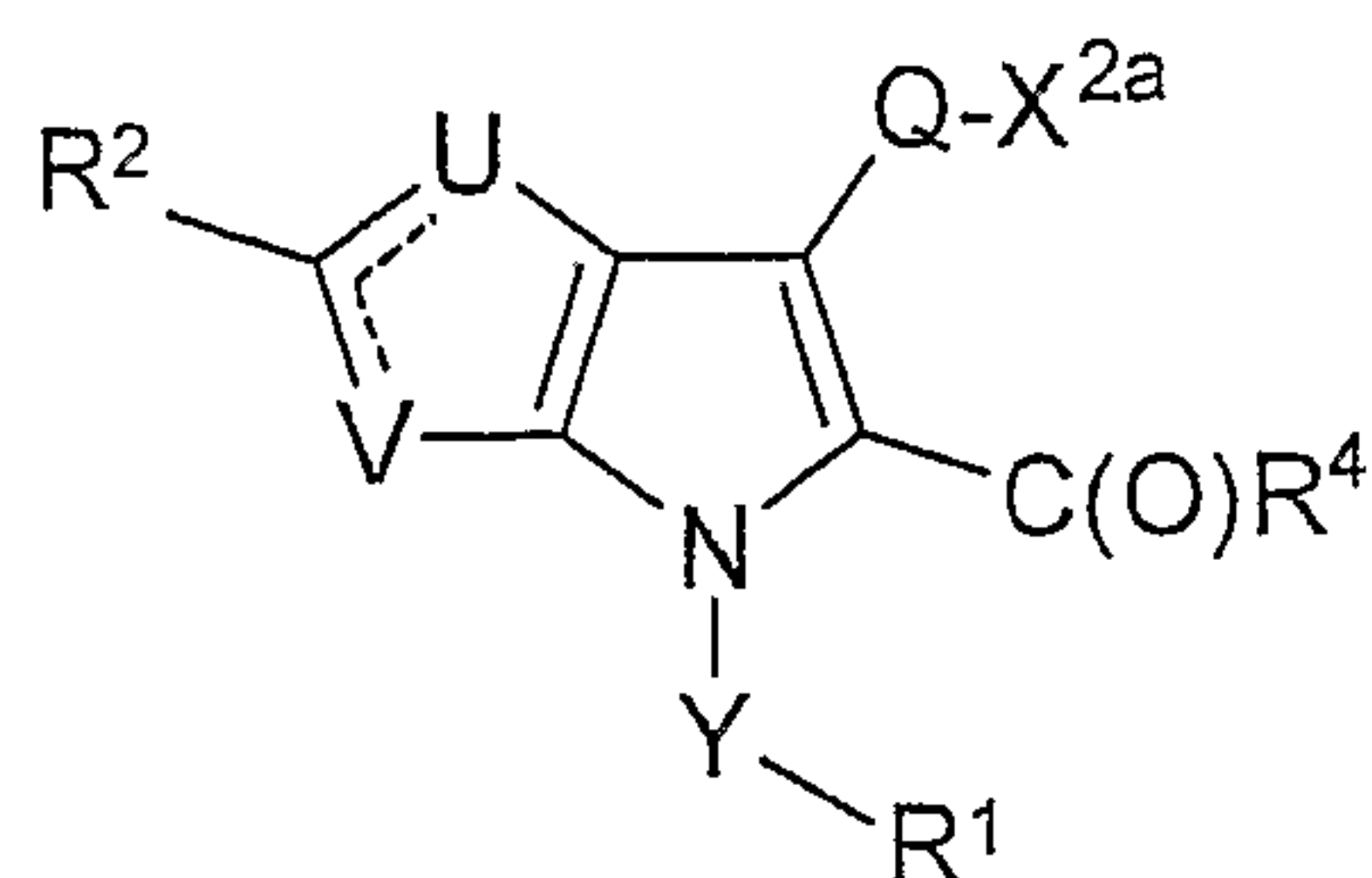
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(vi) for compounds of formula I in which X^1 represents $-Q-X^2$ and Q represents $-S(O)-$ or $-S(O)_2-$, oxidation of a corresponding compound of formula I in which Q represents $-S-$ under appropriate oxidation conditions, which will be known to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

25

(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 $-A^1-R^{14a}$, A^1 represents $-N(R^{15a})A^4-$ 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,

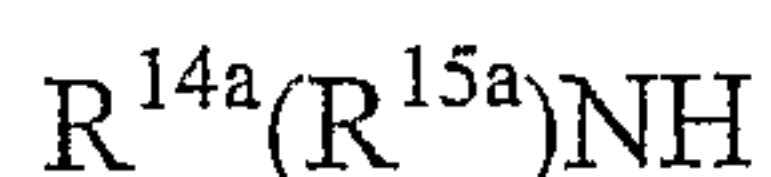
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VII

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 hereinbefore defined, provided that it represents a single bond when X^{2a} represents C_1 alkyl substituted by $=O$ (i.e. $-CHO$), and the dotted lines, U , V , R^1 , R^2 , R^4 and Y are as hereinbefore defined under reductive amination conditions in the presence of a compound of formula VIII,

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VIII

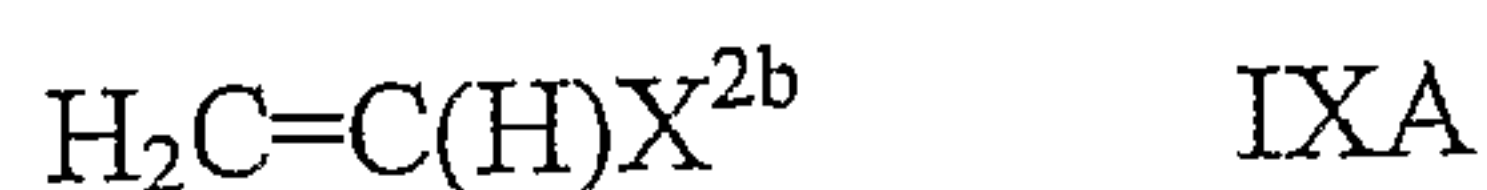
wherein R^{14a} and R^{15a} are as hereinbefore defined, under conditions well known to those skilled in the art;

(vii) 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 $-A^1-R^{14a}$, A^1 represents $-N(R^{15a})A^4$, A^4 is a single bond and R^{14a} and R^{15a} 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^{14a} and R^{15a} 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 and the optional substituents are preferably other than G^1 in which G^1 represents

-A¹-R^{14a}, A¹ represents -OA⁵- or -N(R^{15a})A⁴-, A⁴ and A⁵ both represent a single bond and R^{14a} represents hydrogen), reaction of a corresponding compound of formula IV in which L¹ represents halo (e.g. iodo) with a compound of formula IXA,

5



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,

10



or the like, or a compound of formula IXC,

15



or the like, wherein, in each case, X^{2b} represents H, G¹ (wherein G¹ is preferably other than -A¹-R^{14a} in which A¹ represents -OA⁵- or -N(R^{15a})A⁴-, A⁴ and A⁵ both represent a single bond and R^{14a} represents hydrogen) or C₁₋₆ alkyl optionally substituted with one of more substituents selected from G¹ and/or Z¹ and G¹ and Z¹ 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 PdCl₂(PPh₃)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 standard Horner-Wadsworth-Emmons, or Wittig, reaction conditions, respectively;

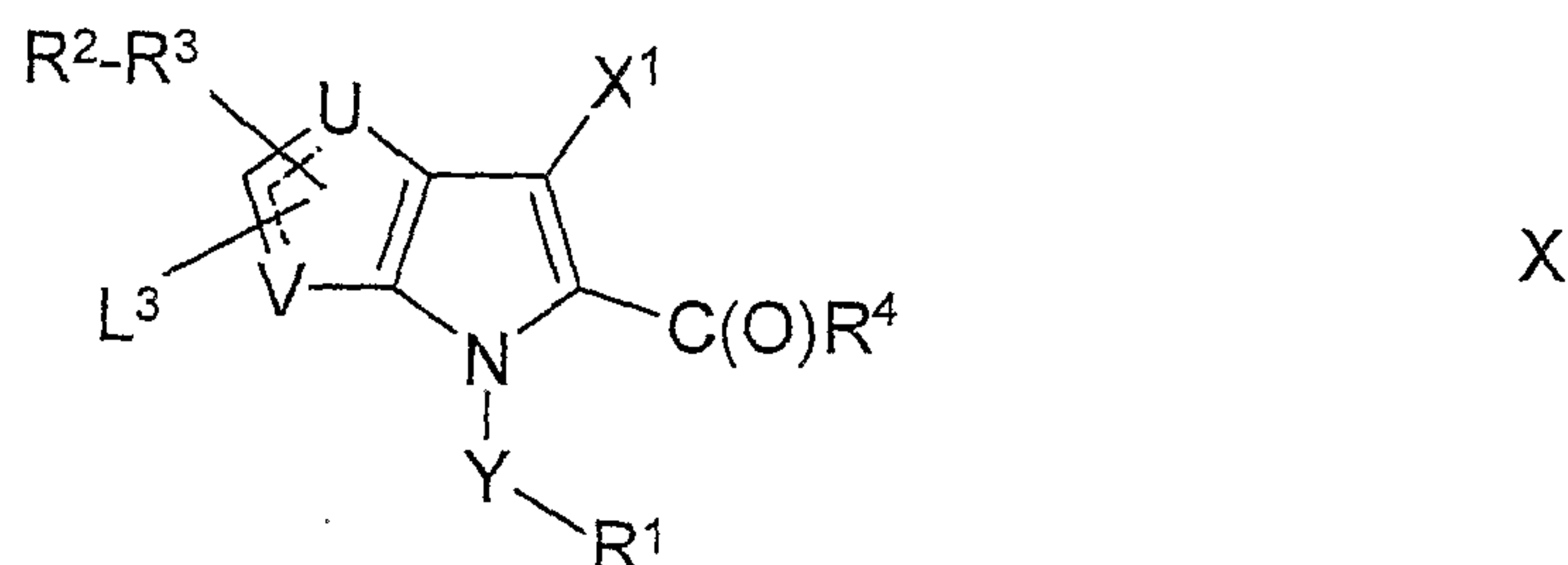
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(ix) for compounds of formula I in which X¹ represents -Q-X² and X² represents optionally substituted, saturated C₂₋₈ alkyl, saturated cycloalkyl, saturated heterocycloalkyl, C₂₋₈ alkenyl, cycloalkenyl or heterocycloalkenyl, reduction (e.g.

30

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
 5 is converted to an alkenyl group, in the presence of an appropriate poisoned catalyst (e.g. Lindlar's catalyst);

(x) for compounds of formula I in which D represents a single bond, $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-4} alkylene or $-S(O)_2-$, reaction of a compound of formula
 10 X,



wherein L^3 represents L^1 or L^2 as hereinbefore defined, which group is attached to
 15 one or both of the two carbon atoms of the thienoid ring of the thienopyrrole, R^2-R^3 represents whichever other substituent on the thienoid ring, i.e. R^2 or R^3 , is already present in that ring, and the dotted lines, U, V, X^1 , R^1 , R^2 , R^3 , R^4 and Y are as hereinbefore defined, with a compound of formula XI,



wherein D^a represents a single bond, $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-4} alkylene or $-S(O)_2-$, L^4 represents L^1 (when L^3 is L^2) or L^2 (when L^3 is L^1) and L^1 , L^2 , E, R^6 and R^7 are as hereinbefore defined. For example, when D^a represents a single
 25 bond, $-C(O)-$ or C_{2-4} alkylene, the reaction may be performed for example under similar conditions to those described hereinbefore in respect of process step (ii) above. Further, when D^a represents $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-4} 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 be activated when L^3 represents halo, by:

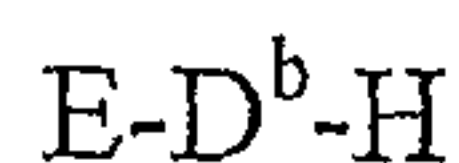
5 (I) forming the corresponding Grignard reagent under standard conditions known to those skilled in the art (e.g. employing magnesium or a suitable reagent such as a mixture of C_{1-6} alkyl-Mg-halide and $ZnCl_2$ or $LiCl$), followed by reaction with a compound of formula XI, optionally in the presence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

10 (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.

15 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 under conditions known to those skilled in the art, for example such as those described hereinbefore in respect of process (ii) above;

20 (xi) for compounds of formula I in which 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 $-B(OH)_2$) with a compound of formula XII,

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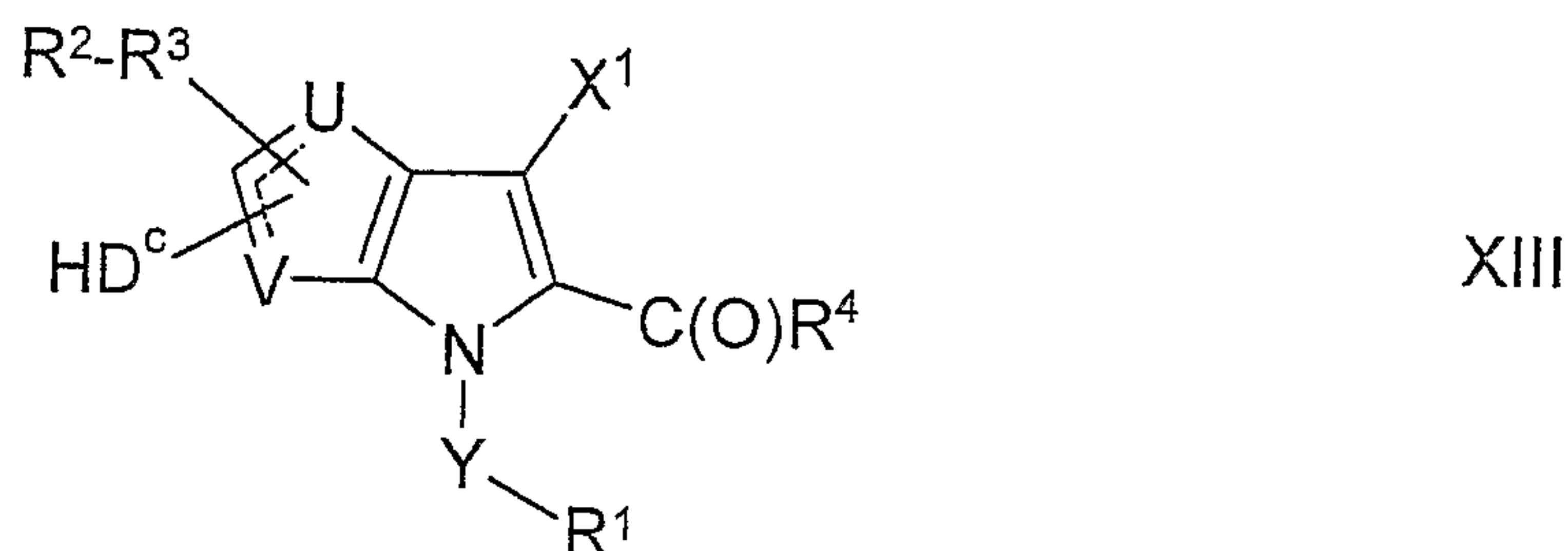
XII

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
30 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

Cu(OAc)₂, a suitable base, such as triethylamine or pyridine, and an appropriate organic solvent, such as DMF or dichloromethane;

(xii) for compounds of formula I in which D represents -S(O)- or -S(O)₂-,
 5 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;

(xiii) for compounds of formula I in which D represents -O- or -S-, reaction of a
 10 compound of formula XIII,

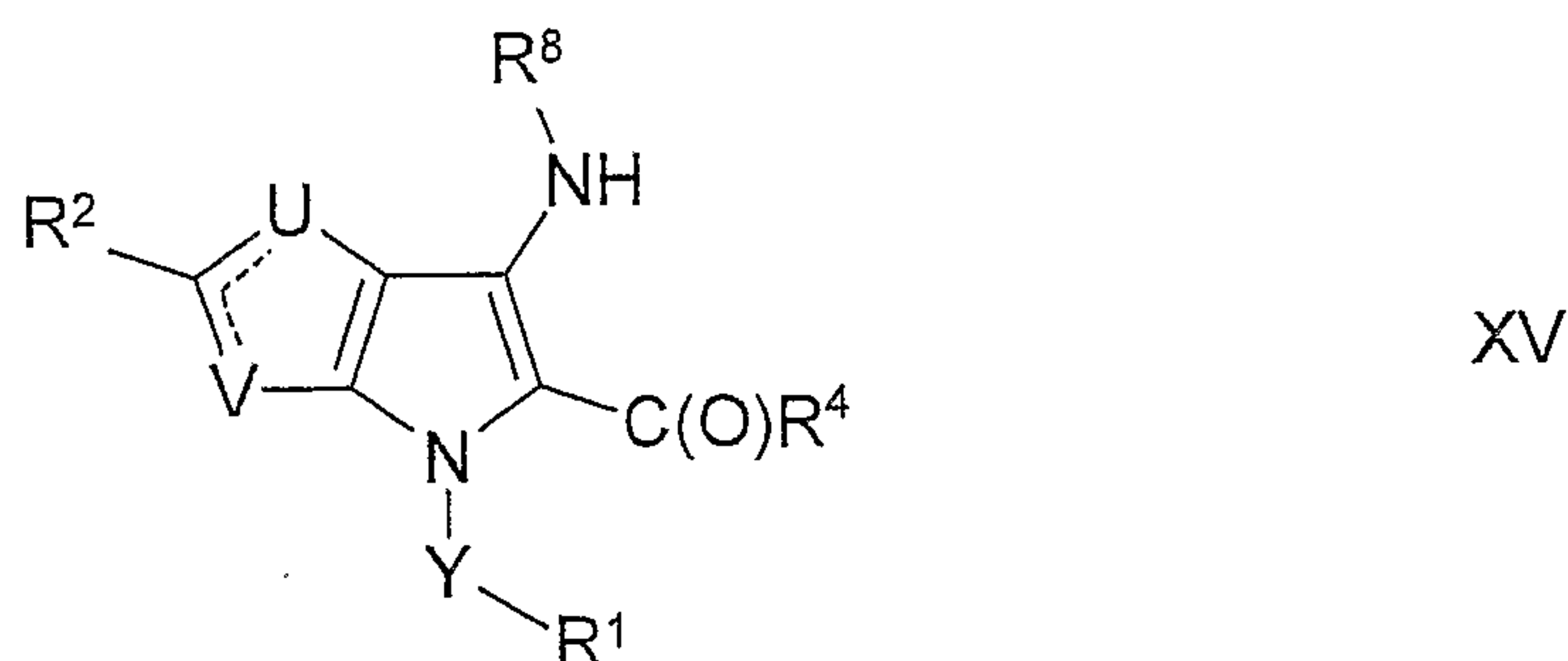


wherein the -D^c-H group is attached to one or both of the two carbon atoms of the
 15 thienoid ring of the thienopyrrole, D^c represents -O- or -S- and the dotted lines, U,
 V, X¹, R¹, R²-R³, R⁴ and Y are as hereinbefore defined, with a compound of
 formula XIV,



20 wherein L² is as hereinbefore defined (for example -B(OH)₂, chloro, bromo or
 iodo) and E is as hereinbefore defined, for example under conditions such as those
 described hereinbefore in respect of process step (ii) above;

25 (xiv) for compounds of formula I in which X¹ represents -N(R⁸)-J-R⁹, reaction of a
 compound of formula XV,



wherein the dotted lines, U, V, R¹, R², R⁴, Y and R⁸ are as hereinbefore defined,
with a compound of formula XVI,

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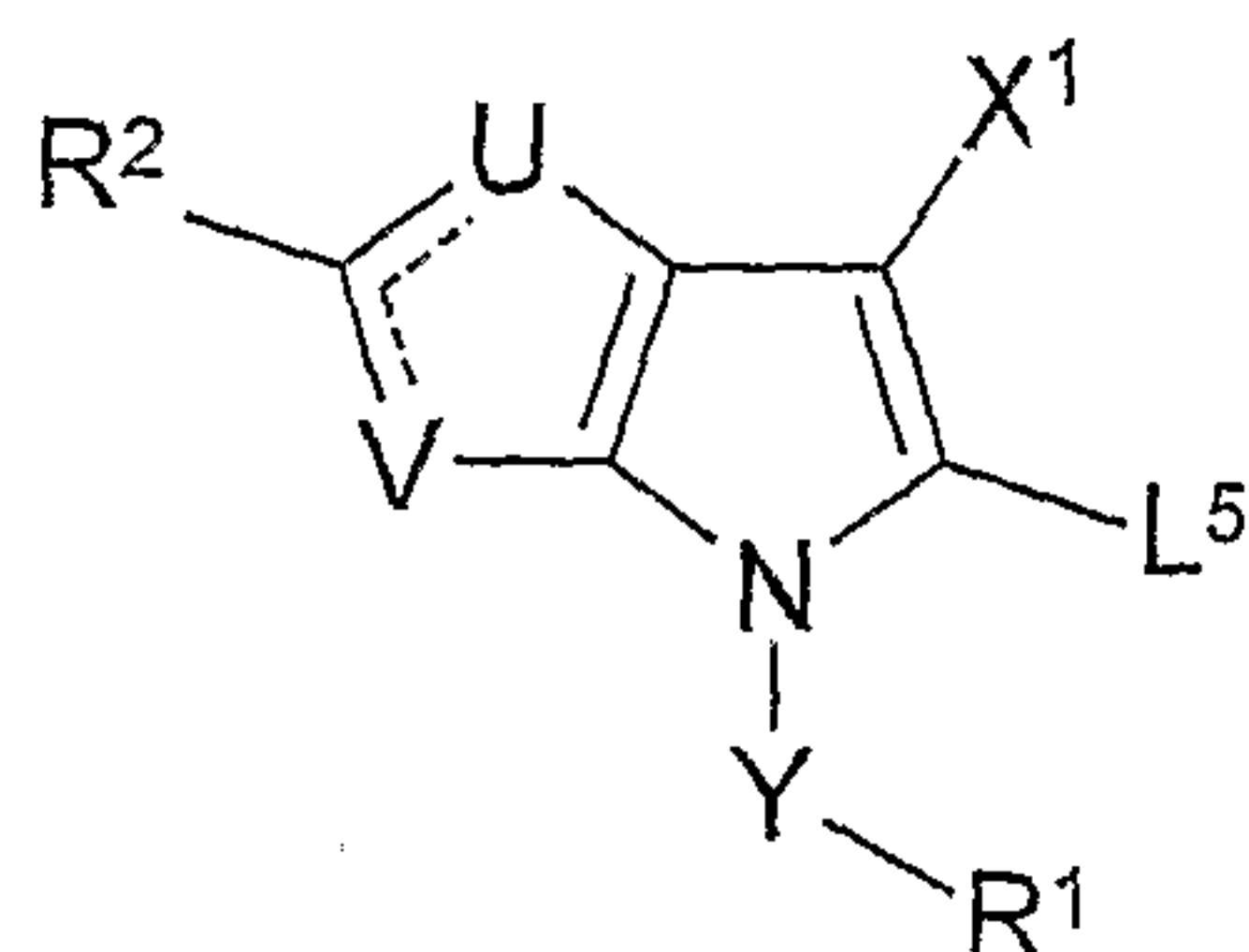


wherein J, R⁹ and L¹ are as hereinbefore defined, for example at around room
temperature or above (e.g. up to 60-70°C) in the presence of a suitable base (e.g.
pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine,
dimethylaminopyridine, diisopropylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene,
sodium hydroxide, or mixtures thereof) and an appropriate solvent (e.g. pyridine,
dichloromethane, chloroform, tetrahydrofuran, dimethylformamide,
dimethylsulfoxide, water, triethylamine or mixtures thereof) and, in the case of
biphasic reaction conditions, optionally in the presence of a phase transfer
catalyst);

(xv) for compounds of formula I in which X¹ represents -N(R⁸)-J-R⁹, J represents
a single bond and R⁹ represents a C₁₋₈ alkyl group, reduction of a corresponding
compound of formula I, in which J represents -C(O)- and R⁹ 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
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 X^1 represents halo, reaction of a compound of formula I wherein X^1 represents H, with a reagent or mixture of reagents known to be a source of halo atoms. For example, for Br atoms, *N*-bromosuccinimide, bromine or 1,2-dibromotetrachloroethane may be employed, for I atoms, iodine, diiodoethane, diiodotetrachloroethane or a mixture of NaI or KI and *N*-chlorosuccinimide may be employed, for Cl atoms, *N*-chlorosuccinimide may be employed and for F atoms, 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), 1-fluoropyridinium triflate, xenon difluoride, CF_3OF 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;

(xvii) for compounds of formula I in which R^4 represents $-OR^{12a}$ in which R^{12a} is other than H, reaction of a compound of formula XVII,



XVII

wherein L^5 represents an appropriate alkali metal group (e.g. sodium, potassium 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, and the dotted lines, U, V, X^1 , R^1 , R^2 and Y are as hereinbefore defined, with a compound of formula XVIII,



XVIII

wherein R^{12za} represents R^{12a} 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;

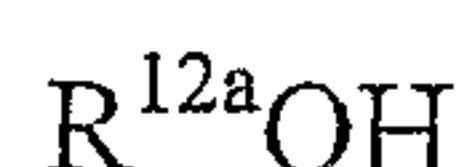
(xviii) for compounds of formula I in which R^4 represents $-OR^{12a}$ and R^{12a} is H, reaction of a compound of formula XVII in which L^5 represents either:

5 (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;

10 (xix) for compounds of formula I in which R^4 represents $-OR^{12a}$, 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
15 compound of formula XIX,



XIX

20 wherein R^{12a} 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^4 represents $-OR^{12a}$ in which R^{12a} represents H, hydrolysis of a corresponding compound of formula I in which R^{12a}
25 does not represent H under standard conditions;

(xxi) for compounds of formula I in which R^4 represents $-OR^{12a}$ and R^{12a} does not represent H:

30 (A) esterification of a corresponding compound of formula I in which R^{12a} represents H; or

(B) trans-esterification of a corresponding compound of formula I in which R^{12a} does not represent H (and does not represent the same value of R^{12a} 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^{12a} represents R^{12za} as hereinbefore defined;

(xxii) for compounds of formula I in which R^4 represents $-N(R^{12b})R^{13b}$, reaction of a corresponding compound of formula I in which R^4 represents $-OR^{12a}$ with a compound of formula XX,

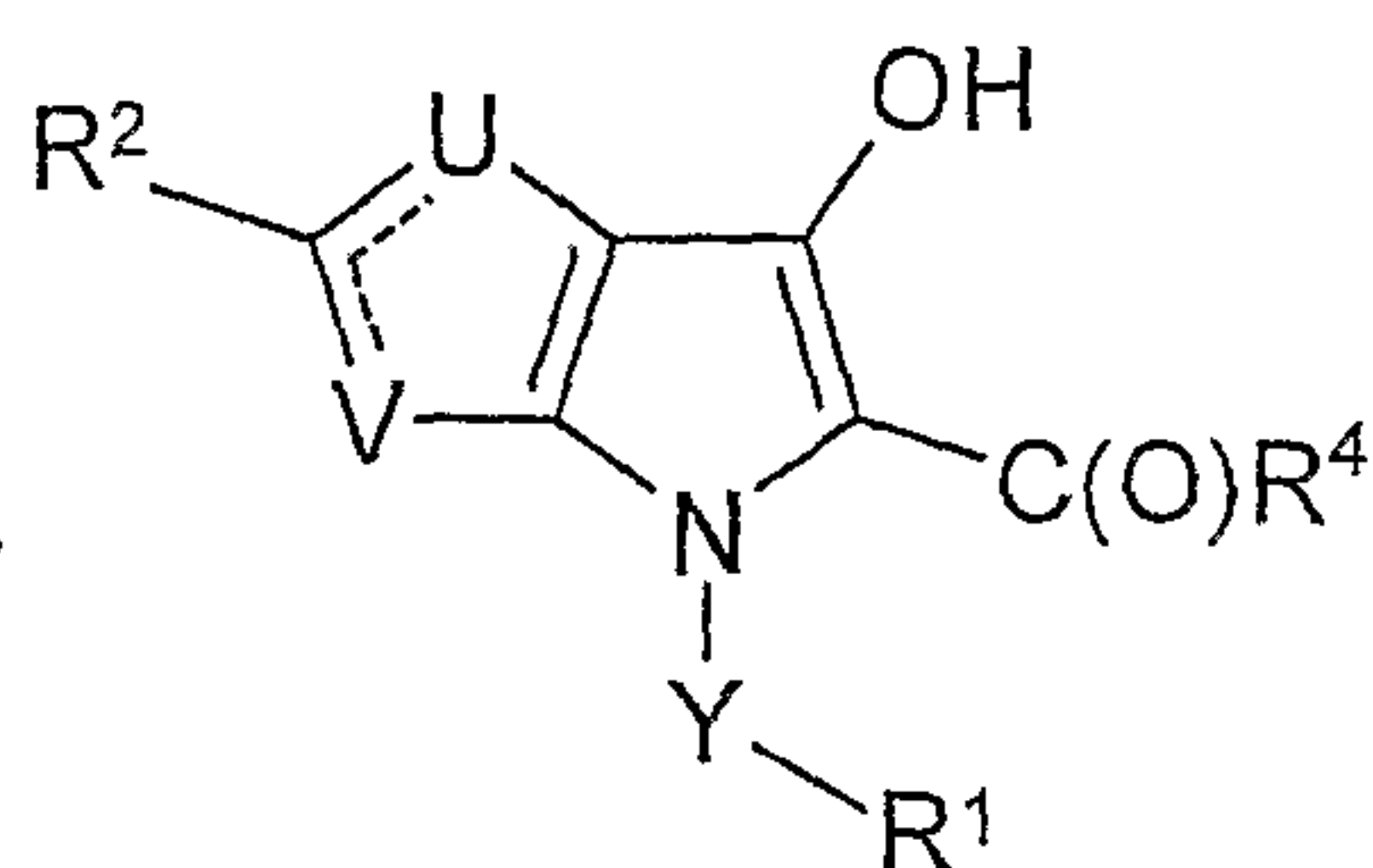


wherein R^{12b} and R^{13b} are as hereinbefore defined under standard conditions. For example, the reaction may be performed in the presence of a suitable coupling reagent (e.g. 1,1'-carbonyldiimidazole, *N,N'*-dicyclohexylcarbodiimide, 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide (or hydrochloride thereof), *N,N'*-disuccinimidyl carbonate, benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro-phosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, benzotriazol-1-yloxytris-pyrrolidinophosphonium hexafluorophosphate, bromotrispyrrolidinophosphonium hexafluorophosphate, 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluorocarbonate or 1-cyclohexylcarbodiimide-3-propyloxymethyl polystyrene, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate or *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate), and/or a suitable base (e.g. sodium hydride, sodium bicarbonate, potassium carbonate, pyrrolidinopyridine, pyridine, triethylamine, tributylamine, trimethylamine, dimethylaminopyridine, diisopropylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene, sodium hydroxide, *N*-ethyldiisopropylamine, *N*-(methylpolystyrene)-4-(methylamino)pyridine, potassium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide, potassium *tert*-butoxide, lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidine, butyllithium (e.g. *n*-, *s*- or *t*-butyllithium) or

mixtures thereof) and an appropriate solvent (e.g. tetrahydrofuran, pyridine, toluene, dichloromethane, chloroform, acetonitrile, dimethylformamide, dimethylsulfoxide, water, triethylamine or mixtures thereof). Alternatively an azodicarboxylate may be employed under Mitsunobo conditions known to those skilled in the art. The skilled person will appreciate that it may be convenient or necessary to first convert the acid or ester compound of formula I to a corresponding acid halide prior to reaction with the compound of formula XX.

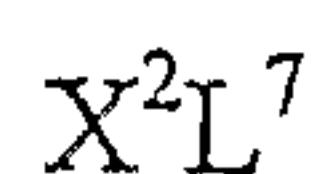
Such conversions may be performed in the presence of a suitable reagent (e.g. oxalyl chloride, thionyl chloride, etc) optionally in the presence of an appropriate solvent (e.g. dichloromethane, THF, toluene or benzene) and a suitable catalyst (e.g. DMF), resulting in the formation of the respective acyl chloride. The skilled person will appreciate that when compounds of formula XX are liquid in nature, they may serve as both solvent and reactant in this reaction. An alternative way of performing this step, includes the reaction of a compound of formula I in which R^4 represents $-OR^{12a}$ in which R^{12a} is other than H (e.g. ethyl) with a compound of formula XX, in the presence of, e.g. trimethylaluminium, for example in an inert atmosphere and in the presence of a suitable solvent (e.g. dichloromethane);

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



XXI

wherein the dotted lines, U, V, R^1 , R^2 , R^4 and Y are as hereinbefore defined, with a compound of formula XXII,



XXII

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;

5

(xxiv) for compounds of formula I in which X^1 represents $-N(R^8)-J-R^9$, reaction of a compound of formula XXI as hereinbefore defined, with a compound of formula VI in which X^{1b} represents $-N(R^8)-J-R^9$ and R^8 , R^9 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 $MgCl_2$));

(xxv) 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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);

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(xxvi) 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 (e.g. α to the indole ring) by a G^1 substituent in which G^1 represents $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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 derivative of a compound of formula V in which L^2 represents chloro, bromo or

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iodo, Q^a is a single bond and X^2 represents C_{1-7} alkyl, under conditions known to those skilled in the art;

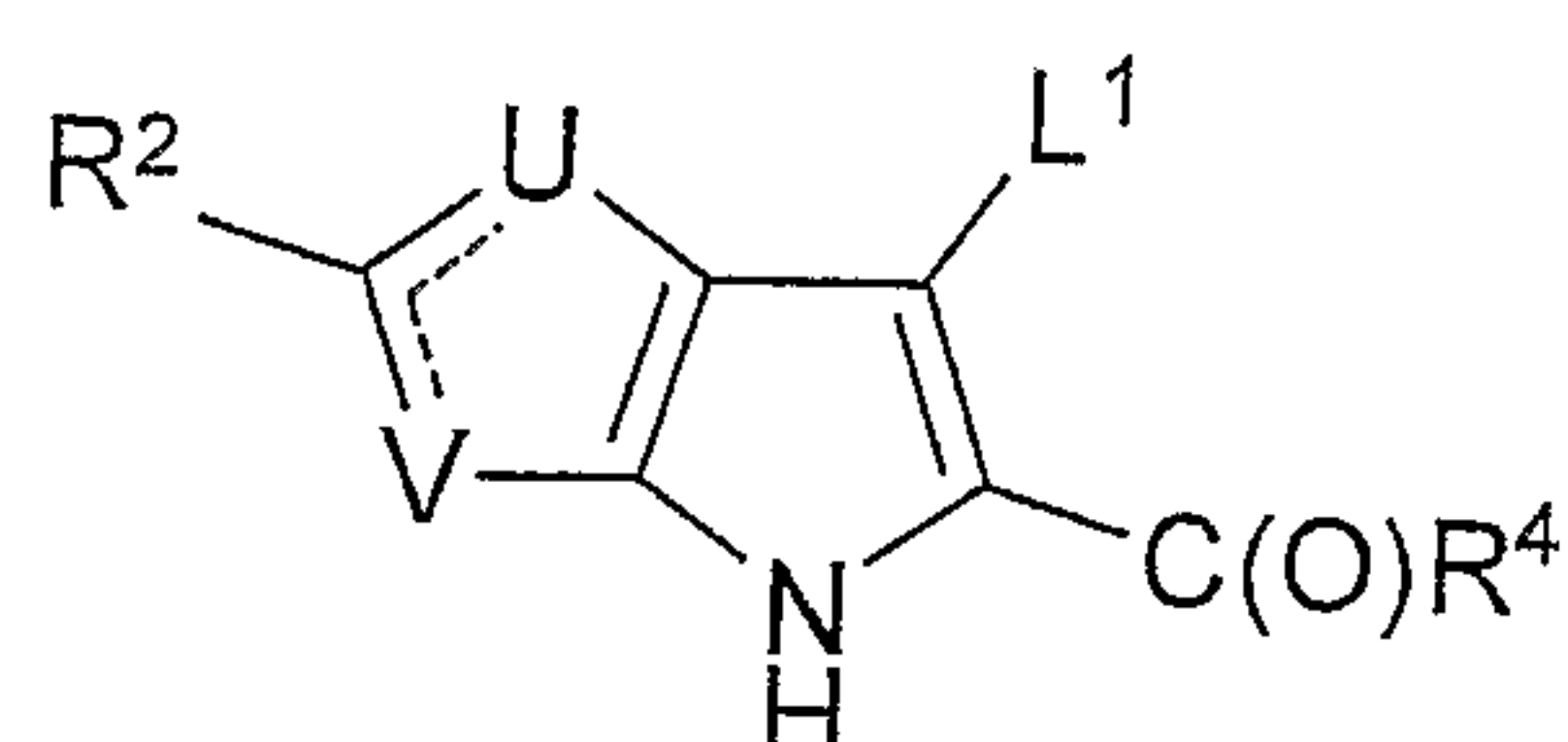
(xxvii) for compounds of formula I in which X^1 represents $-Q-X^2$, Q represents a single bond, and X^2 represents C_{1-8} alkyl or heterocycloalkyl, both of which are unsubstituted in the position α to the indole ring, reduction of a corresponding compound of formula I in which X^2 represents C_{1-8} alkyl substituted α to the indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{14a}$, A^1 represents $-OA^5$, A^5 represents a single bond and R^{14a} represents H, in the presence of a 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); or

(xxviii) 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 $=O$ under conditions known to those skilled in the art, for example $NaBH_4$ 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.

Compounds of formula II may be prepared by:

(a) reaction of a compound of formula XXIII,

38



XXIII

wherein the dotted lines, U, V, L¹, R² and R⁴ are as hereinbefore defined, with, for compounds of formula II in which X¹ represents:

- (1) -Q-X² and Q represents a single bond or -C(O)-, a compound of formula V as hereinbefore defined; or
- (2) -N(R⁸)-J-R⁹ or -Q-X², 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;

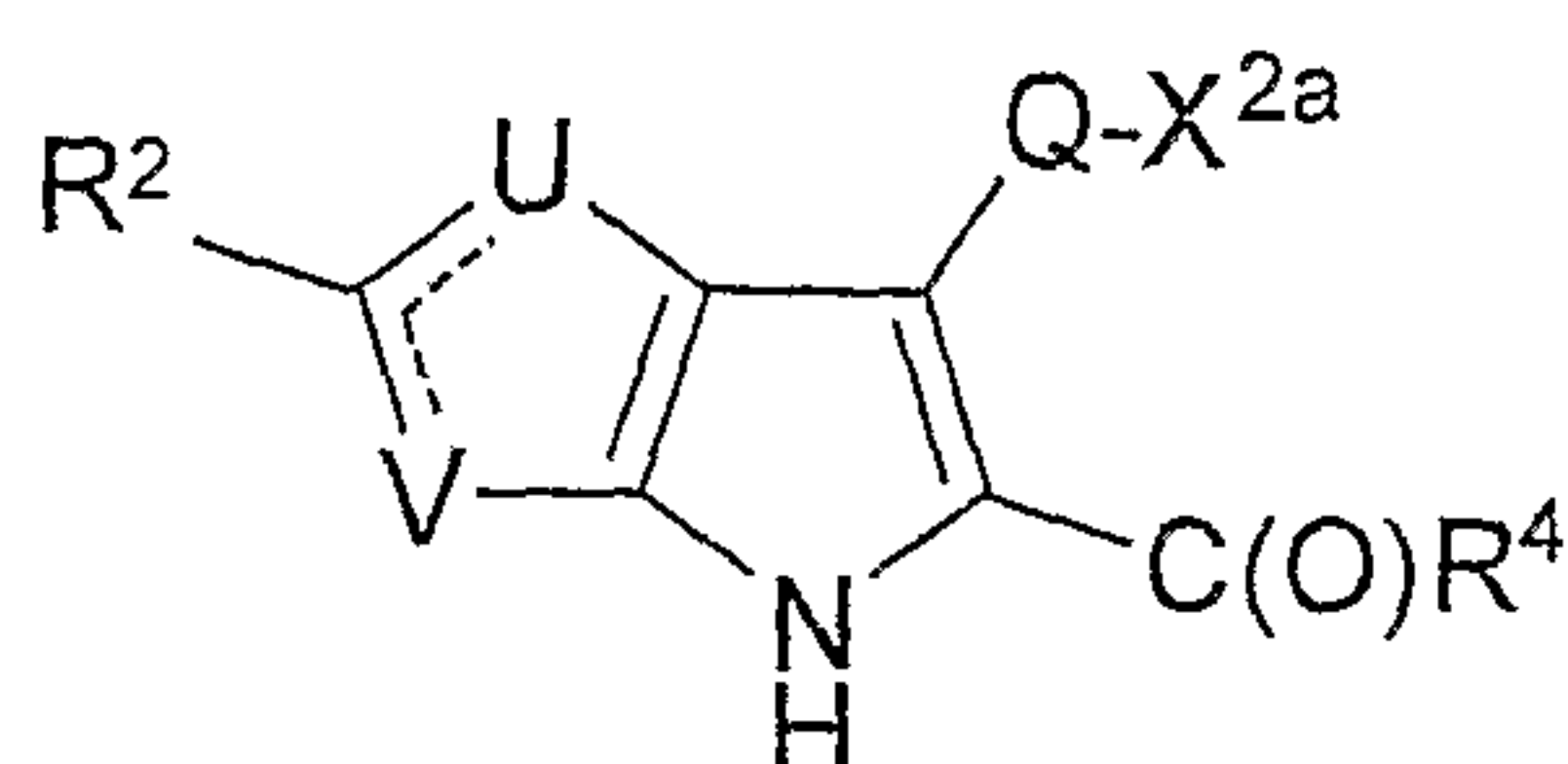
- (b) for compounds of formula II in which X¹ represents -Q-X² and Q represents -C(O)-, reaction of a corresponding compound of formula II in which X¹ represents H with a compound of formula V in which Q^a represents -C(O)- and L² represents a suitable leaving group, for example under conditions such as those described in respect of preparation of compounds of formula I (process (iii)) above.

- (c) for compounds of formula II in which X¹ represents -Q-X² and Q represents -S-, reaction of a corresponding compound of formula II in which X¹ represents H with a compound of formula VI in which X^{1b} represents -Q-X² 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;

- (d) for compounds of formula II in which X¹ represents -Q-X² and Q represents -S(O)- or -S(O)₂-, oxidation a

corresponding compound of formula II in which Q represent
-S-;

- (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 $-A^1-R^{14a}$, A^1 represents $-N(R^{15a})A^4-$ 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 XXIV,



XXIV

wherein the dotted lines, U, V, Q, X^{2a} , R^2 and R^4 are as hereinbefore defined by reductive amination in the presence of a compound of formula VIII as hereinbefore defined;

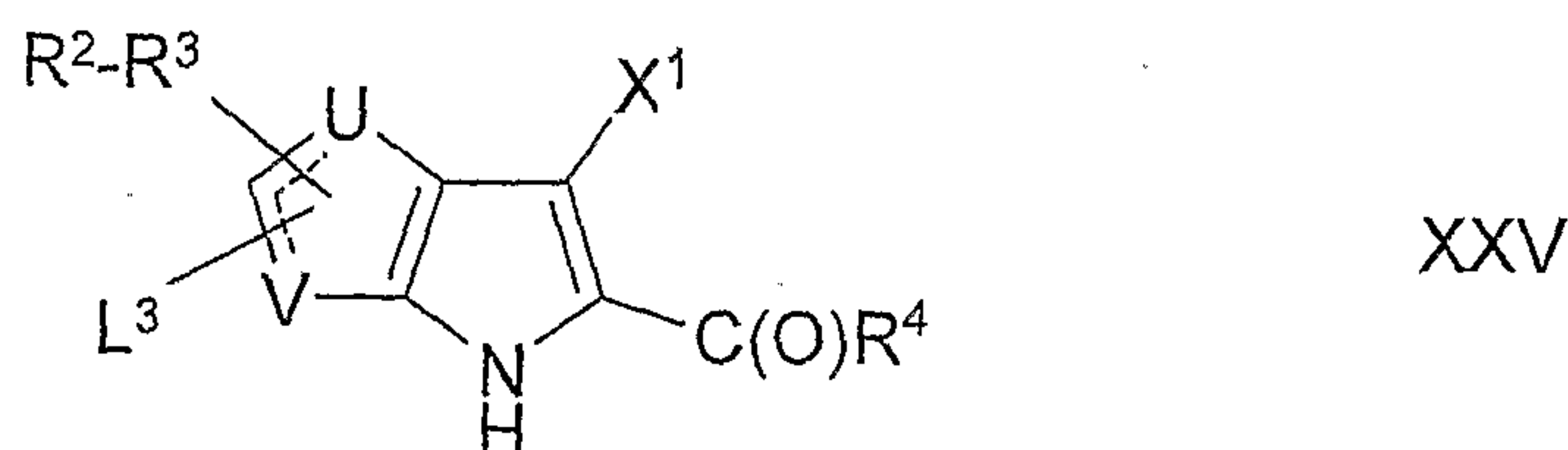
- (ea) for compounds of formula II in which X^1 represents $-Q-X^2$, Q represents a single bond, X^2 represents methyl substituted by G^1 , G^1 represents $-A^1-R^{14a}$, A^1 represents $-N(R^{15a})A^4-$, A^4 is a single bond and R^{14a} and R^{15a} are preferably methyl, reaction of a corresponding compound of formula II in which X^1 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 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 and the optional

substituents are preferably other than G^1 in which G^1 represents $-A^1-R^{14a}$, A^1 represents $-OA^5-$ or $-N(R^{15a})A^4-$, A^4 and A^5 both represent a single bond and R^{14a} represents hydrogen), reaction of a compound of formula XXIII in which L^1 represents halo (e.g. iodo) with a compound of formula IXA as hereinbefore defined, or a compound of formula XXIV 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 D represents a single bond, $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-8} alkylene or $-S(O)_2-$, reaction of a compound of formula XXV,



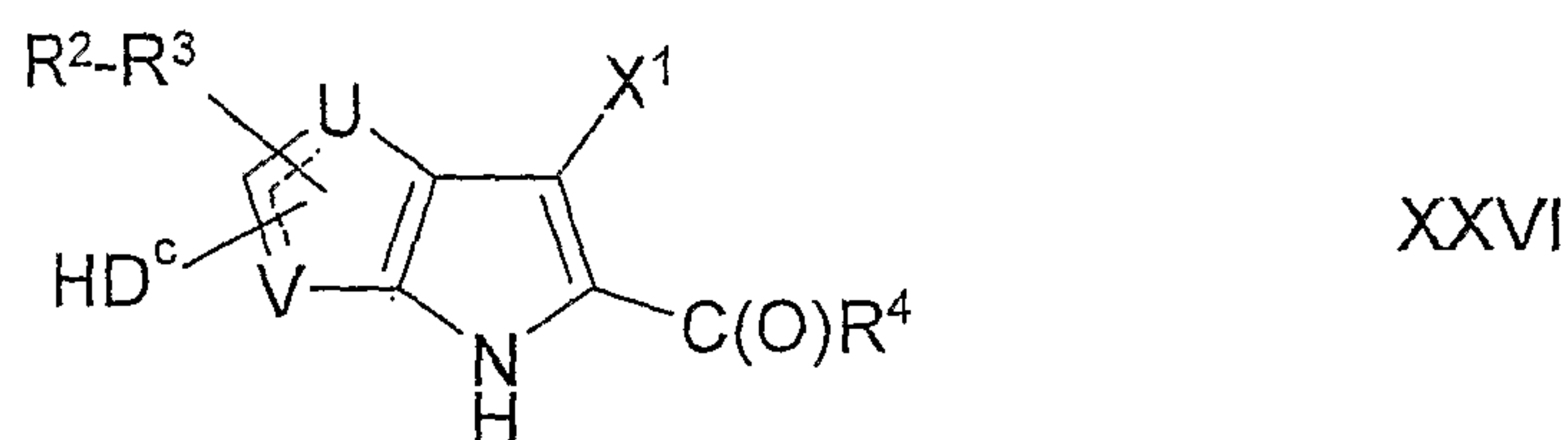
wherein the dotted lines, U , V , X^1 , L^3 , R^2-R^3 and R^4 are as hereinbefore defined with a compound of formula XI as

hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (x)) above;

- 5 (i) for compounds of formula II in which D represents -S-, -O- or C₂₋₄ alkynylene in which the triple bond is adjacent to E, reaction of a compound of formula XXV as hereinbefore defined in which L³ represents L² as hereinbefore defined (for example -B(OH)₂) with a compound of formula XII as hereinbefore defined, for example
10 under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xi)) above;

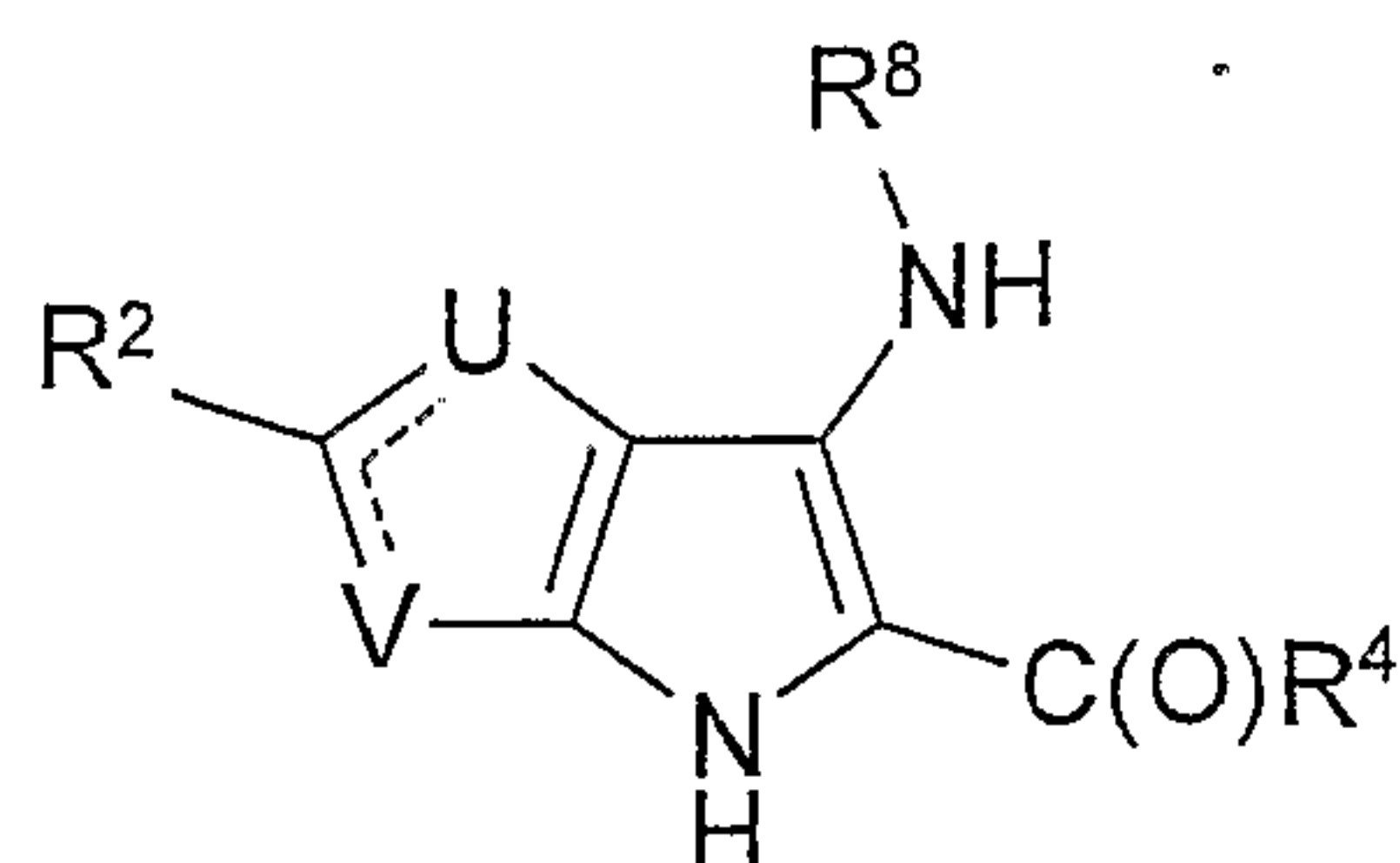
- 15 (j) for compounds of formula II in which D represents -S(O)- or -S(O)₂-, oxidation of a corresponding compound of formula II in which D represents -S-;

- 20 (k) for compounds of formula II in which D represents -O- or -S-, reaction of a compound of formula XXVI,



- 25 wherein D^c, the dotted lines, U, V, X¹, R²-R³ and R⁴ are as hereinbefore defined, with a compound of formula XIV as hereinbefore defined;

- (l) for compounds of formula II in which X¹ represents -N(R⁸)-J-R⁹, reaction of a compound of formula XXVII,



XXVII

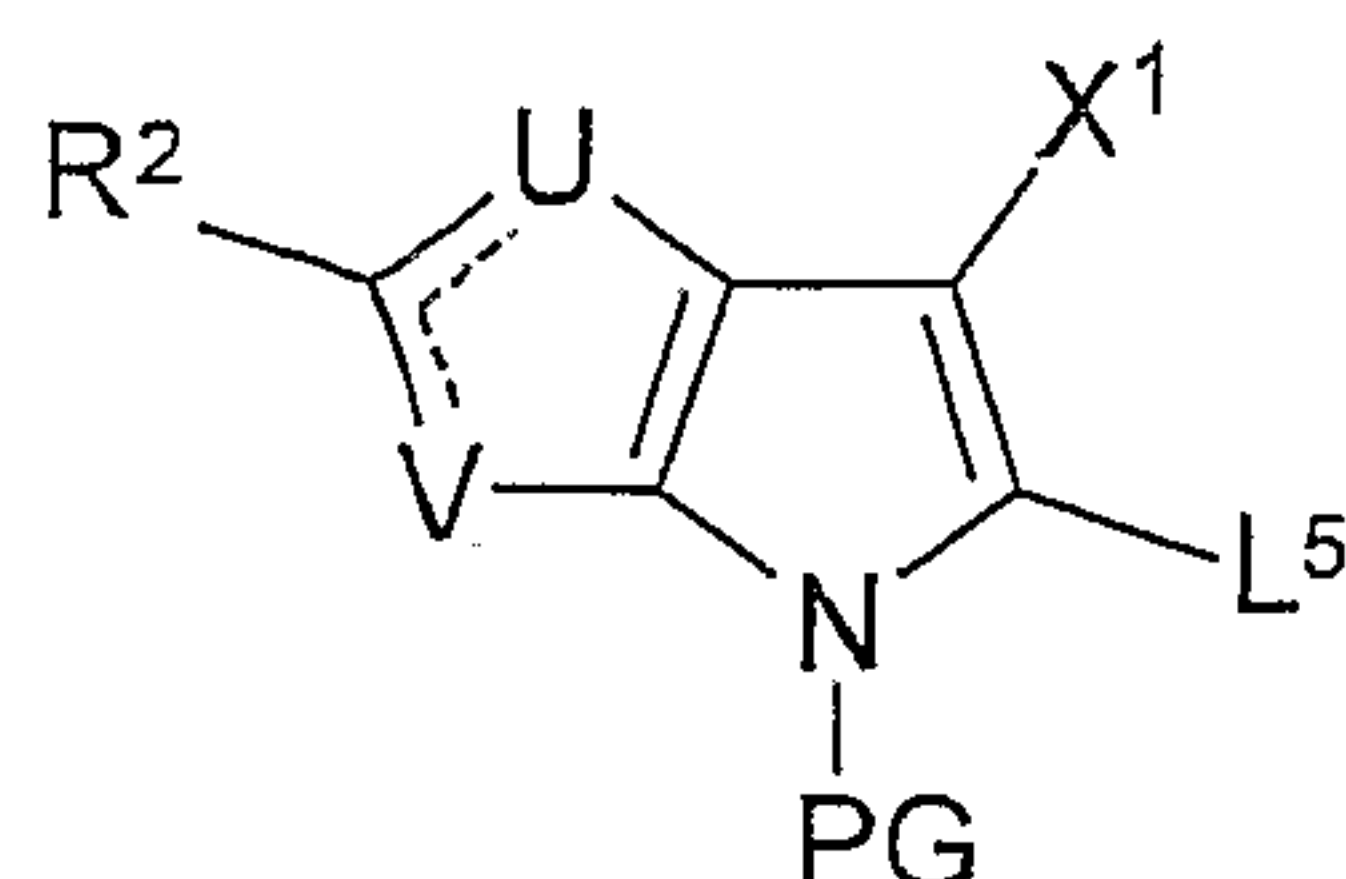
wherein the dotted lines, U, V, R², R⁴ and R⁸ are as hereinbefore defined with a compound of formula XVI as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xiv)) above;

(m) for compounds of formula II in which X¹ represents -N(R⁸)-J-R⁹, J represents a single bond and R⁹ represents a C₁₋₈ alkyl group, reduction of a corresponding compound of formula II, in which J represents -C(O)- and R⁹ represents H or a C₁₋₇ alkyl group, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xv)) above;

(n) for compounds of formula II in which X¹ represents halo, reaction of a compound of formula II wherein X¹ represents H, with a reagent or mixture of reagents known to be a source of halo 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 R⁴ represents -OR^{12a} and R^{12a} is other than H, reaction of a compound of formula XXVIII,

43



XXVIII

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 the dotted lines, U, V, L⁵, X¹ and R² 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;

(p) for compounds of formula II in which R⁴ represents -OR^{12a} in which R^{12a} represents H, reaction of a compound of formula XXVIII in which L⁵ represents an alkali metal, or -Mg-halide, with carbon dioxide, followed by acidification;

(q) for compounds of formula II in which R⁴ represents -OR^{12a}, reaction of a corresponding compound of formula XXVIII in which L⁵ 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;

(r) for compounds of formula II in which R⁴ represents -OR^{12a} in which R^{12a} represents H, hydrolysis of a corresponding compound of formula II in which R^{12a} does not represent H;

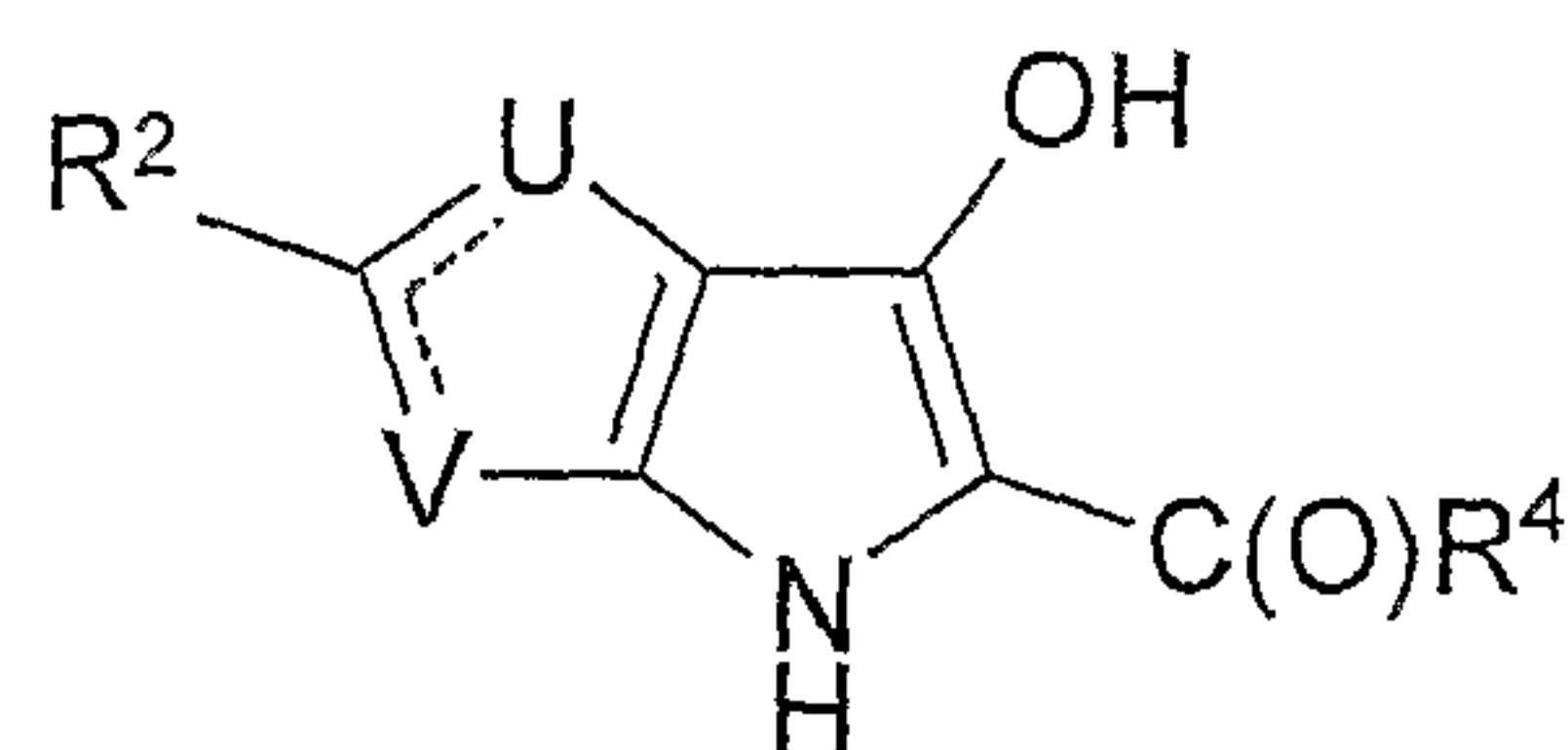
(s) for compounds of formula II in which R⁴ represents -OR^{12a} in which R^{12a} does not represent H:

(A) esterification of a corresponding compound of formula II in which R^{12a} represents H; or

(B) trans-esterification of a corresponding compound of formula II in which R^{12a} does not represent H (and does not represent the same value of R^{12a} as the compound of formula II to be prepared);

(t) for compounds of formula II in which R^4 represents $-N(R^{12b})R^{13b}$, reaction of a corresponding compound of formula II in which R^4 represents $-OR^{12a}$ with a compound of formula XX 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;

(u) for compounds of formula II in which X^1 represents $-Q-X^2$ in which Q represents $-O-$, reaction of a compound of formula XXIX,



XXIX

wherein the dotted lines, U, V, R^2 and R^4 are as hereinbefore defined, with a compound of formula XXII as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxiii)) above;

(v) for compounds of formula II in which X^1 represents $-N(R^8)-J-R^9$, reaction of a compound of formula XXIX as hereinbefore defined, with a compound of formula VI in which X^{1b} represents $-N(R^8)-J-R^9$ and R^8 , R^9 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 (xxiv)) above;

- 5 (w) 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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 (xxv)) above;
- 10
- 15
- 20 (x) 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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;
- 25
- 30 (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, 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 indole ring by a G^1 substituent in which G^1 represents $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} represents H, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (process (xxvii)) above; or

- (z) 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 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 (xxviii)) above.

Compounds of formula IV may be prepared as follows:

- (a) Reaction of a compound of formula XXIII as hereinbefore defined with a compound of formula XXX,

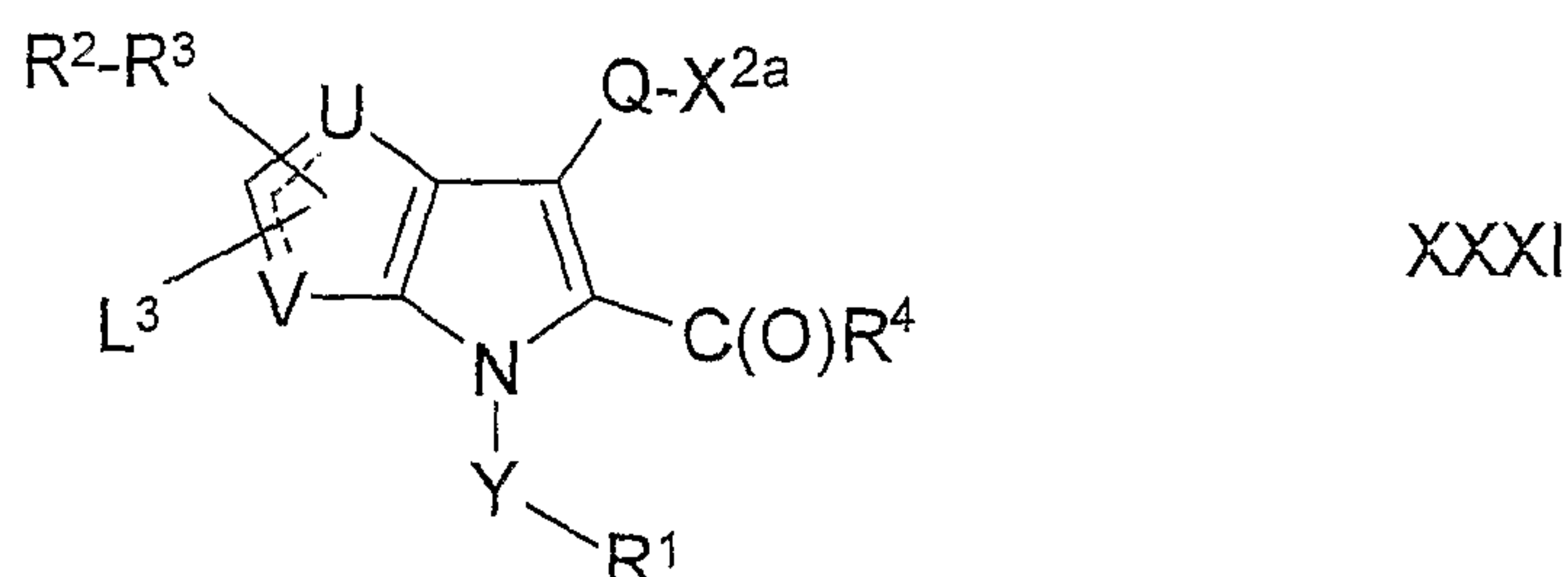


wherein R^1 and L^2 are as hereinbefore defined or a compound of formula III as hereinbefore defined, for example under reaction conditions similar to those described hereinbefore in respect of preparation of compounds of formula I (processes (ii) and (i), respectively) above; or

- (b) for compounds of formula IV wherein L^1 represents a sulfonate group, reaction of a compound of formula XXI as hereinbefore defined with an appropriate reagent for the conversion of the hydroxyl group to the sulfonate group (e.g. tosyl chloride, mesyl chloride, triflic anhydride and the like) under conditions known to those skilled in the art.

Compounds of formula VII may be prepared by:

- (a) For compounds of formula VII in which D represents a single bond, $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-4} alkylene or $-S(O)_2-$, reaction of a compound of formula XXXI,



- wherein the dotted lines, U, V, Q, X^{2a} , L^3 , Y, R^1 , R^2-R^3 and R^4 are as hereinbefore defined (L^3 in particular may represent halo, such as bromo) with a compound of formula XI as hereinbefore defined (in which L^4 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;

- (b) 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); or

- (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 X^1 represents H with a mixture of DMF and, for example, oxalyl chloride, phosgene or $P(O)Cl_3$ (or the like) in an appropriate solvent system (e.g. DMF or dichloromethane).

Compounds of formula X may be prepared by reaction of a compound of formula XXV 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.

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

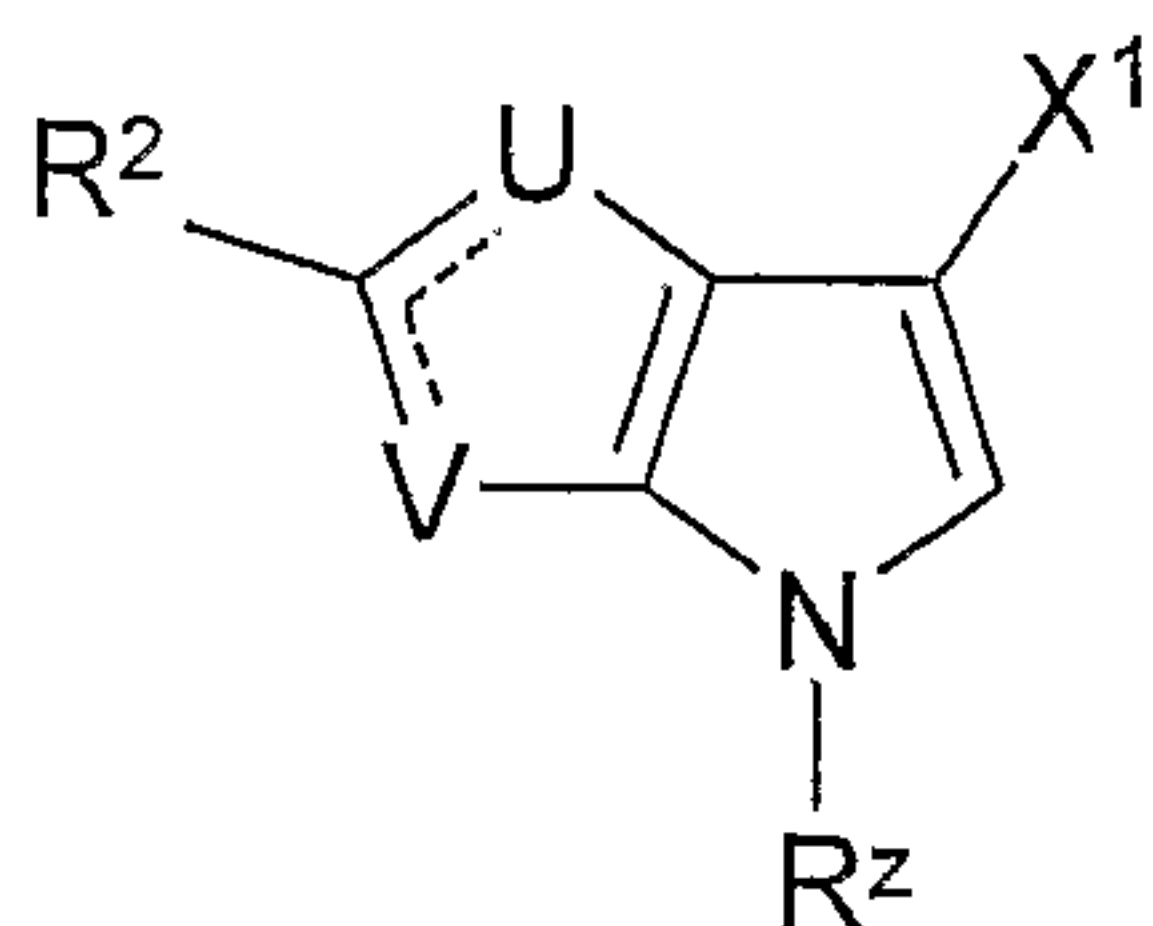
Compounds of formulae XV and XXVII may be prepared by reaction of a corresponding compound of formula IV, or XXIII, respectively, with a compound of formula XXXII,



XXXII

wherein R^8 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).

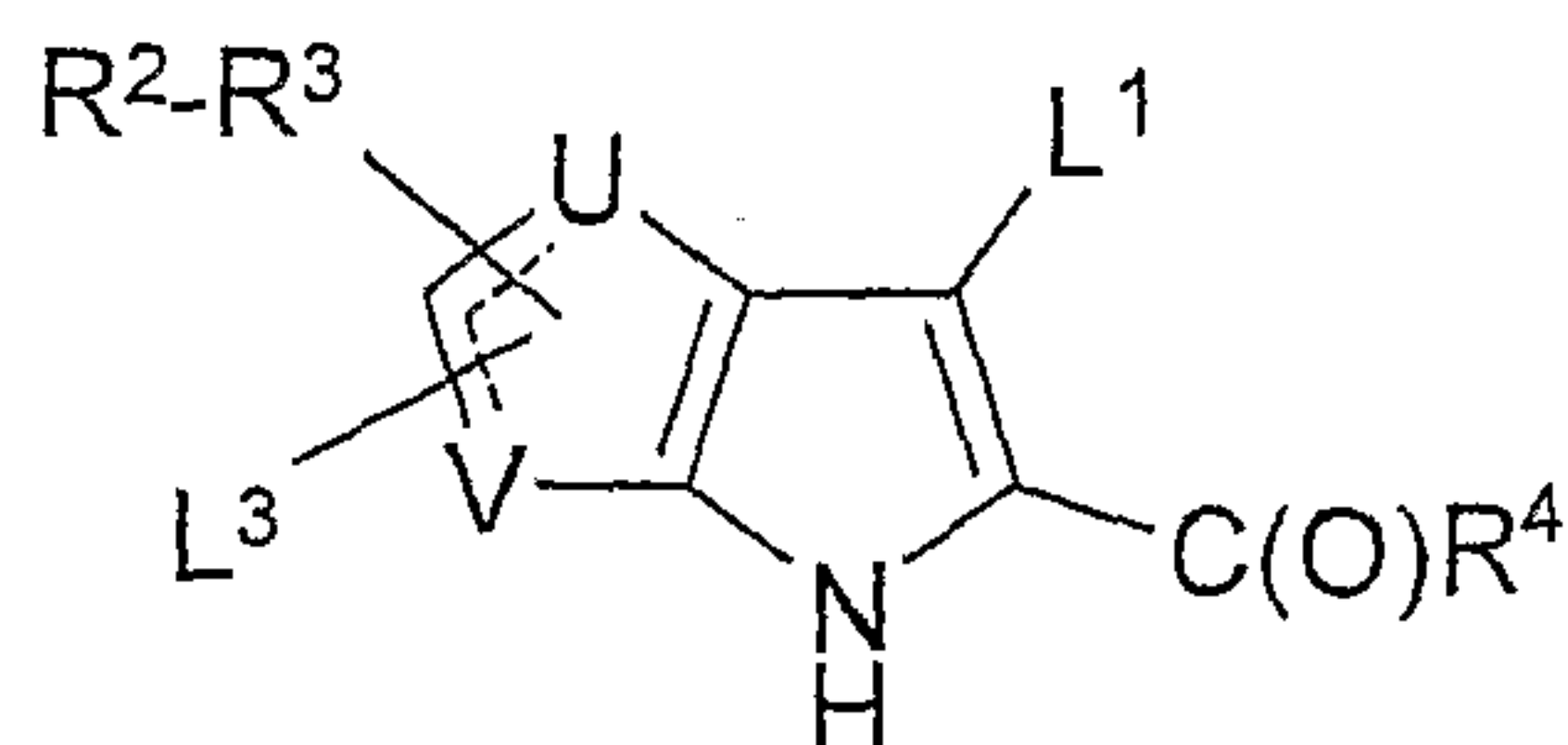
Compounds of formulae XVII and XXVIII in which L^5 represents an appropriate alkali metal, such as lithium may be prepared by reaction of a compound of formula XXXIII,



XXXIII

wherein R^2 represents $-Y-R^1$ (in the case of a compound of formula XVII) or PG (in the case of a compound of formula XXVIII), and the dotted lines, U, V, PG, X^1 , Y, R^1 and R^2 are as hereinbefore defined, with an appropriate base, such as lithium diisopropylamide or BuLi under standard conditions. Compounds of formulae XVII and XXVIII in which L^5 represents $-Mg$ -halide may be prepared from a corresponding compound of formula XVII or XXVIII (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 XXVIII in which L^5 represents, for example, a zinc-based group, halo or a boronic acid group, may be prepared by reacting a corresponding compound of formula XVII or XXVIII 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 XXIII may be prepared by standard techniques. For example compounds of formula XXIII in which D represents a single bond, $-C(O)-$, $-C(R^6)(R^7)-$, C_{2-4} alkylene or $-S(O)_2-$ may be prepared by reaction of a compound of formula XXXIV,



XXXIV

wherein the dotted lines, U, V, L¹, L³, R²-R³ and R⁴ are as hereinbefore defined
 5 with a compound of formula XI 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 XXIV and XXXI, in which Q represents a single bond
 10 and X^{2a} represents -CHO, may be prepared from compounds of formulae II, or X,
 respectively, in which X¹ represents H, by reaction 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) for example as described
 hereinbefore.

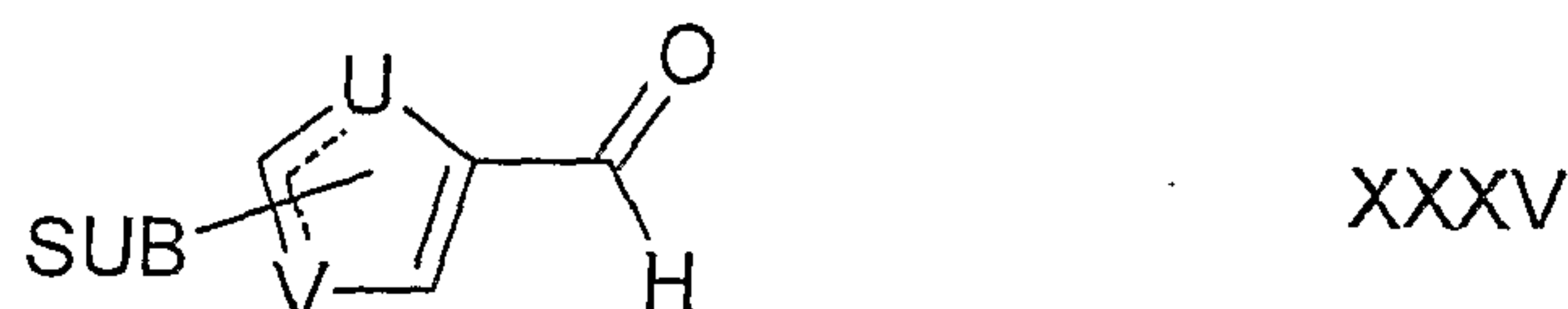
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Compounds of formulae III, V, VI, VIII, IXA, IXB, IXC, XI, XII, XIII, XIV,
 XVI, XVIII, XIX, XX, XXI, XXII, XXV, XXVI, XXIX, XXX, XXXII, XXXIII
 and XXXIV are either commercially available, are known in the literature, or may
 be obtained either by analogy with the processes described herein, or by
 20 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.

25 Thienopyrroles of formulae II, IV, VII, X, XIII, XV, XVII, XXI, XXIII, XXIV,
 XXV, XXVI, XXVII, XXVIII, XXIX, XXXI, XXXIII and XXXIV may also be
 prepared with reference to a standard heterocyclic chemistry textbook (e.g.
 "Heterocyclic Chemistry" by J. A. Joule, K. Mills and G. F. Smith, 3rd edition,
 published by Chapman & Hall or "Comprehensive Heterocyclic Chemistry II" by

A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, 1996) and/or made according to the following general procedures.

For example, compounds of formulae II, XXV and XXVI in which X¹ represents
5 H may be prepared by reaction of a compound of formula XXXV,



wherein SUB represents the substitution pattern that is present in the relevant
10 compound to be formed (i.e. the compound of formula II, XXV or XXVI, respectively), with a compound of formula XXXVI,



15 wherein R⁴ is as hereinbefore defined and preferably -OR^{12a}, in which R^{12a} is as hereinbefore defined and preferably R^{12za} as hereinbefore defined, under conditions known to the person skilled in the art (i.e. conditions to induce a condensation reaction, followed by a thermally induced cyclisation).

20 Compounds of formulae XXXV and XXXVI 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
25 may refer to *inter alia* "Comprehensive Organic Synthesis" by B. M. Trost and I. Fleming, Pergamon Press, 1991.

The substituents X¹, R¹, R², R³ and R⁴ in final compounds of the invention or relevant intermediates may be modified one or more times, after or during the
30 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^4 represents $-OR^{12a}$, in which R^{12a} 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^{12a} will be hydrogen). In this respect, the skilled person may also refer to "*Comprehensive Organic Functional Group Transformations*" by A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Pergamon Press, 1995.

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

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

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

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

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

The use of protecting groups is fully described in "*Protective Groups in Organic Chemistry*", edited by J W F McOmie, Plenum Press (1973), and "*Protective*

Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Medical and Pharmaceutical Uses

5

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 proviso (a), for use as a pharmaceutical.

10 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
15 (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.

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

25

Furthermore, certain compounds of the invention (including, but not limited to, compounds of formula I in which R^4 represents $-OR^{12a}$ and R^{12a} 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
30 form compounds of the invention that possess pharmacological activity as such (including, but not limited to, corresponding compounds of formula I, in which R^4 represents $-OR^{12a}$ and R^{12a} represents hydrogen). Such compounds (which also includes compounds that may possess some pharmacological activity, but that

activity is appreciably lower than that of the "active" compounds of the invention to which they are metabolised), may also be described as "prodrugs".

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

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

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
15 of mPGES-1 or a complex of which the mPGES-1 enzyme forms a part, and/or may elicit a mPGES-1 modulating effect, for example as may be demonstrated in the test described below. Compounds of the invention may thus be useful in the treatment of those conditions in which inhibition of a PGES, and particularly mPGES-1, is required.

20

Compounds of the invention may inhibit the activity of leukotriene C₄ (LTC₄), for example as may be shown in a test such as that described in *Eur. J. Biochem.*, **208**, 725-734 (1992), and may thus be useful in the treatment of those conditions in which inhibition of LTC₄ is required. Compounds of the invention may also
25 inhibit the activity of 5-lipoxygenase-activating protein (FLAP), for example as may be shown in a test such as that described in *Mol. Pharmacol.*, **41**, 873-879 (1992).

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

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

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

Accordingly, compounds of the invention may be useful in the treatment of 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 (such as 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 a 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 proviso (a), 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.

5 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.

10 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
15 hereinbefore defined but without proviso (a), 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).

20

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 in particular proviso (a); and
- 25 (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
30 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).

5 Thus, there is further provided:

(1) a pharmaceutical formulation including a compound of the invention, as hereinbefore defined but without the provisos and in particular proviso (a), another therapeutic agent that is useful in the treatment of inflammation, and a
10 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 and in particular proviso (a),
15 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,

20 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
25 body weight per day (mg/kg/day) to about 100 mg/kg/day, preferably about 0.01 to about 10 mg/kg/day, and more preferably about 0.1 to about 5.0 mg/kg/day. For e.g. oral administration, the compositions typically contain between about 0.01 mg to about 500 mg, and preferably between about 1 mg to about 100 mg, of the active ingredient. Intravenously, the most preferred doses will range from
30 about 0.001 to about 10 mg/kg/hour during constant rate infusion. Advantageously, compounds may be administered in a single daily dose, or the

total daily dosage may be administered in divided doses of two, three or four times daily.

5 In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the route of administration, the type and severity of the condition that is to be treated, as well as the species, age, weight, sex, renal function, hepatic function and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual
10 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
15 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.

20 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)
25 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

30 In the assay mPGES-1 catalyses the reaction where the substrate PGH₂ is converted to PGE₂. 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 H₂O / MeCN (7/3), containing FeCl₂ (25 mM) and HCl (0.15 M). The assay is performed at room temperature in 96-well plates. Analysis of the amount of PGE₂ is performed with reversed phase HPLC (Waters 2795
 5 equipped with a 3.9 x 150 mm C18 column). The mobile phase consists of H₂O / 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
 10 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 PGH₂ solution. Incubation of the plate at room temperature for 60 seconds.
 - 15 4. 100 µL stop solution.
- 180 µL per sample is analyzed with HPLC.

Examples

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

AcOH	acetic acid
DMF	dimethylformamide
DMSO	dimethylsulfoxide
25 EtOAc	ethyl acetate
MeCN	acetonitrile
NMR	nuclear magnetic resonance
rt	room temperature
TFA	trifluoroacetic acid
30 THF	tetrahydrofuran

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

Preparation 1

5 2-Bromo-6-iodo-4-(3-phenylpropyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

(a) 2-Bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A solution of 5-bromothiophene-2-carboxaldehyde (9.55 g, 50.0 mmol) and azidoacetic acid ethyl ester (28.6 g, 200.0 mmol) in absolute EtOH (50 mL) was added to a stirred solution of NaOEt (2.3 M in EtOH, 87 mL, 200 mmol) in EtOH (100 mL). The mixture was stirred at -25 °C for 20 h and poured into NH₄Cl (aq, sat) cooled to 0° C. The suspension was extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (Na₂SO₄), concentrated and purified by chromatography to afford 2-azido-3-(4-bromothiophen-2-yl)acrylic acid ethyl ester as a yellow oil. The oil was dissolved in *o*-xylene (50 mL) which was added dropwise to *o*-xylene (50 mL) at reflux. After cooling, the precipitate was filtered off to give the sub-title compound (5.81 g, 36%)

(b) 2-Bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

20 A solution of NaI (1.8 g, 12.3 mmol) in acetone (100 mL) was added dropwise to a stirred solution of *N*-chlorosuccinimide (1.6 g, 12.3 mmol) in acetone (30 mL) protected from light, followed after 15 min by the dropwise addition of 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (2.8 g, 10.3 mmol; see step (a) above) in acetone (100 mL). After 30 min at rt the mixture was poured into Na₂S₂O₃ (aq, 10%, 140 mL) and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (Na₂SO₄), concentrated and purified by chromatography to give the sub-title compound (3.78 g, 92%).

30 (c) 2-Bromo-6-iodo-4-(3-phenylpropyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A solution of 2-bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (400 mg, 1.0 mmol; see step (b) above) in DMF (4 mL) was added carefully to a

stirred suspension of NaH (75% in mineral oil, 39 mg, 1.2 mmol) in DMF (2 mL) at 0°C. The mixture was stirred at 0°C for 30 min. A solution of 1-bromo-3-phenylpropane (182 µL, 1.2 mmol) in DMF (4 mL) was added in portions. The mixture was stirred at rt for 12 h, poured into H₂O and extracted with *t*-BuOMe. The combined extracts were washed with H₂O and brine, dried (Na₂SO₄), concentrated and purified by chromatography to yield the sub-title compound (147 mg, 28%).

(d) 2-Bromo-6-iodo-4-(3-phenylpropyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

- 10 A mixture of 2-bromo-6-iodo-4-(3-phenylpropyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (147 mg, 0.28 mmol; see step (c)), aqueous NaOH (aq, 1 M, 1.5 mL) and MeCN (3.0 mL) was heated at 110 °C for 20 min. The mixture was allowed to cool, acidified with HCl (aq, 1 M) to pH 2 and filtered. The solid was recrystallised from EtOH to give the title compound (55 mg, 40 %).
- 15 200 MHz ¹H NMR (acetone-*d*₆, ppm) δ 11.7-11.2 (1H, br s) 7.46 (1H, s) 7.31-7.11 (5H, m) 4.67-4.59 (2H, m) 2.70-2.62 (2H, m) 2.21-2.08 (2H, m)

Preparation 2

2-Bromo-6-iodo-4-(4-phenoxybutyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

- 20 The title compound was prepared in accordance with Example 1, steps (c) and (d) from 2-bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester and (4-bromobutoxy)benzene.
- 200 MHz ¹H NMR (DMSO-*d*₆, ppm) δ 13.14 (1H, s) 7.77 (1H, s) 7.29-7.19 (2H, m) 6.92-6.84 (3H, m) 4.57-4.49 (2H, m) 3.90 (2H, t, *J* = 6.3 Hz) 1.88-1.72 (2H, m) 1.68-1.52 (2H, m).

Preparation 3

4-[3,5-Bis(trifluoromethyl)benzyl]-2-bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid

- 30 The title compound was prepared in accordance with Example 1, steps (c) and (d) from 2-bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester and 1-bromomethyl-3,5-bis(trifluoromethyl)benzene.

200 MHz ^1H NMR (acetone- d_6 , ppm) δ 11.8-11.4 (1H, br s) 7.96 (1H, s) 7.85 (2H, s) 7.70 (1H, s) 6.05 (2H, s).

Preparation 4

5 3-Bromo-6-iodo-4-(4-phenoxybutyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Preparation 1 from 4-bromothiophene-2-carboxaldehyde.

^1H NMR (DMSO- d_6 , 200 MHz): δ 13.31 (1H, s) 7.75 (1H, s) 7.29-7.19 (2H, m) 6.92-6.84 (3H, m) 4.84-4.76 (2H, m) 3.93 (2H, t, $J = 6.3$ Hz) 1.95-1.80 (2H, m)
10 1.75-1.61 (2H, m).

Example 1

4-(3-Chlorobenzyl)-2,6-bis-(4-trifluoromethoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

15

(a) 2-Bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid

Method A

2-Bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (1.50 g, 3.75 mmol; see Preparation 1, step (b)) in DMF (10 mL) was added carefully to a
20 stirred suspension of NaH (75% in mineral oil, 150 mg, 4.69 mmol) in DMF (10 mL) at 0°C. The mixture was stirred at 0°C for 30 min and a solution of 3-chlorobenzyl chloride (595 μL , 4.69 mmol) in DMF (10 mL) was added in portions. The mixture was stirred at rt for 12 h, poured into H_2O and extracted with *t*-BuOMe. The combined extracts were washed with H_2O and brine, dried
25 (Na_2SO_4), concentrated and recrystallised from MeOH to yield the sub-title compound (1.1 g, 57%).

Method B

2-Bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (480 g, 1.2
30 mmol; see Preparation 1, step (b)), 3-chlorobenzyl chloride (0.23g, 1.4 mmol), NaI (450 mg, 3 mmol), K_2CO_3 (410 mg, 2.8 mmol), and 18-crown-6 (22 mg, 0.1 mmol) were dissolved in anhydrous toluene (50 mL) and heated at reflux for 12 h.

The mixture was filtered, concentrated and purified by chromatography to afford 470 mg (74%) of the sub-title compound.

5 (b) 4-(3-Chlorobenzyl)-2,6-bis-(4-trifluoromethoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

10 K_3PO_4 (720 mg, 3.4 mmol), $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) and di-(*tert*-butyl)-bicyclohexylphosphine (53.6 mg, 0.18 mmol) were added to a solution of 2-bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (262.3 mg, 0.5 mmol; see step (a) above) and 4-trifluoromethoxyphenylboronic acid (309 mg, 1.5 mmol) in toluene (10 mL). The mixture was heated at reflux for 14 h under argon, poured into Na_2CO_3 (aq, 10%, 50 mL) and extracted with EtOAc. The combined extracts were dried ($MgSO_4$), concentrated and purified by chromatography, affording 173 mg (54%) of the sub-title product.

15 (c) 4-(3-Chlorobenzyl)-2,6-bis-(4-trifluoromethoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

20 A mixture of 4-(3-chlorobenzyl)-2,6-bis-(4-trifluoromethoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (134 mg, 0.21 mmol; see step (b) above), KOH (aq, 1 M, 1.5 mL) and MeCN (5 mL) was heated at reflux for 24 h. The mixture was poured into H_2O (10 mL) and acidified to pH 5 with HCl (aq, conc). The precipitate was filtered off and washed with H_2O (100 mL) to yield 78 mg (61%) of the title compound.

25 200 MHz ^1H -NMR ($DMSO-d_6$, ppm) δ 12.75-12.55 (1H, br s) 7.97 (1H, s) 7.85-7.78 (2H, m) 7.73-7.67 (2H, m) 7.46-7.32 (7H, m) 7.19-7.11 (1H, m) 5.82 (2H, s).

Example 2

2,6-Bis-(4-*tert*-butylphenyl)-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

5 (a) 2,6-Bis-(4-*tert*-butylphenyl)-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1, step (b) from 2-bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester and 4-*tert*-butylphenylboronic acid.

10

(b) 2,6-Bis-(4-*tert*-butylphenyl)-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

A mixture of 2,6-bis-(4-*tert*-butylphenyl)-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (163 mg, 0.28 mmol; see step (a) above), KOH (aq, 2 M, 2.0 mL) and dioxane (3.0 mL) was heated by microwave irradiation at 120 °C for 5 h. The mixture was acidified with HCl (aq, conc) and the precipitate was filtered off and washed with H₂O (50 mL) to yield 114 mg (73%) of the title compound.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.75-12.55 (1H, br s) 7.80 (1H, s) 7.62-7.57 (2H, m) 7.51-7.27 (9H, m) 7.13-7.08 (1H, m) 5.79 (2H, s) 1.31 (9H, s) 1.27 (9H, s).

Example 3

4-(3-Chlorobenzyl)-2,6-bis(phenylethynyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid (2-methoxyethyl)amide

(a) 2-Bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid.

The sub-title compound was prepared in accordance with Example 2, step (b) from 2-bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 1, step (a) above).

(b) 2-Bromo-4-(3-chlorobenzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid (2-methoxyethyl)amide

SOCl₂ (73 μL, 1.0 mmol) was added to 2-bromo-4-(3-chlorobenzyl)-6-iodo-
thieno[3,2-*b*]pyrrole-5-carboxylic acid (487.0 mg, 0.97 mmol; see step (a) above)
5 in CH₂Cl₂ and stirred for 2 h at rt. The mixture was concentrated and
methoxyethylamine (105 μL, 1.2 mmol) in toluene (10 mL) was added. After
stirring for 4 h at rt, the mixture was concentrated and purified by chromatography
affording 193 mg (32%) of the sub-title compound.

10 (c) 4-(3-Chlorobenzyl)-2,6-bis-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid (2-methoxyethyl)amide

Pd(PPh₃)₄ (12 mg, 0.01 mmol) was added to a solution of 2-bromo-4-(3-chloro-
benzyl)-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid (2-methoxyethyl)amide
(166.1 mg, 0.3 mmol; see step (b) above) and phenylethynyltrimethylstannane
15 (185.4 mg, 0.7 mmol) in toluene (3.0 mL) and the mixture was heated at reflux for
2 h, poured into Na₂CO₃ (aq, sat, 20 mL) and extracted with EtOAc. The
combined extracts were dried (MgSO₄), concentrated and purified by
chromatography to afford the title compound (59 mg, 36%).

¹H-NMR (200 MHz DMSO-*d*₆, ppm) δ 7.89-7.83 (1H, m) 7.64-7.58 (2H, m) 7.51-
20 7.48 (2H, m) 7.39-7.34 (6H, m) 7.23-7.21 (2H, m) 7.15 (1H, s) 7.04-7.02 (2H, m)
5.83 (2H, s) 3.69-3.62 (2H, m) 3.51 (2H, t, *J* = 5.1 Hz) 3.16 (3H, s).

Example 4

25 4-(3-Chlorobenzyl)-6-iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

(a) 2-(5-Methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A mixture of 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (1.0 g, 3.6
mmol; see Preparation 1, step (a)), hexamethyldisilazane (1.7 mL, 8.0 mmol) and
30 THF (4 mL) was heated at reflux for 2 h under argon. The mixture was
concentrated and (5-methylthien-2-yl)tributylstannane (1.7 g, 4.4 mmol),
Pd(PPh₃)₄ (250 mg, 0.22 mmol) and toluene (5 mL) were added. The mixture was

heated at reflux for 3 h, poured into Na₂CO₃ (aq, sat, 20 mL) and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (MgSO₄), concentrated and purified by chromatography, yielding the sub-title compound (670 mg, 64%).

5

(b) 6-Iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Preparation 1, step (b) from 2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see

10

step (a) above).

(c) 4-(3-Chlorobenzyl)-6-iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1, step (a) from

15

6-iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above) and 3-chlorobenzyl chloride.

(d) 4-(3-Chlorobenzyl)-6-iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

20

The title compound was prepared in accordance with Example 2, step (b) from 4-(3-chlorobenzyl)-6-iodo-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (c) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.3-12.9 (1H, br s) 7.59 (1H, s) 7.34-7.32 (2H, m) 7.22 (1H, s) 7.16 (1H, d, *J* = 3.5 Hz) 7.04-6.97 (1H, m) 6.80 (1H, d, *J* =

25

3.5 Hz) 5.81 (2H, s) 2.45 (3H, s).

Example 54-(3-Chlorobenzyl)-2-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid(a) 2-Bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

5 The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1, step (a)) and 3-chlorobenzyl chloride.

(b) 4-(3-Chlorobenzyl)-2-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

10 Pd(PPh₃)₄ (60 mg, 0.052 mmol) and AsPh₃ (60 mg, 0.2 mmol) was added to a solution of 2-bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (399 mg, 1.0 mmol; see step (a) above) and phenylethynyltrimethylstannane (318 mg, 1.2 mmol) in toluene (3 mL). The
15 mixture was heated at reflux for 4 h, poured into Na₂CO₃ (aq, sat, 20 mL) and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (MgSO₄), concentrated and purified by chromatography yielding the sub-title compound (370 mg, 88%)

(c) 4-(3-Chlorobenzyl)-2-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid

A solution of 4-(3-chlorobenzyl)-2-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (120 mg, 0.29 mmol; see step (b) above) in dioxane (3 mL) and KOH (aq, 4 M, 1 mL, 4 mmol) was heated at reflux for 4 h. The mixture was acidified with HCl (aq, conc) and filtered. The solid was washed with water (50
25 mL) and recrystallised from EtOH to yield 86 mg (76%) of the title compound.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.68 (1H, s) 7.56-7.53 (2H, m) 7.46-7.42 (3H, m) 7.36-7.33 (2H, m) 7.25 (1H, s) 7.22 (1H, s) 7.09-7.05 (1H, m) 5.78 (2H, s).

Example 64-(3-Chlorobenzyl)-2-cyclohex-1-enylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, steps (b) and (c) from 2-bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester see step (a), Example 5) and cyclohex-1-enylethynyltrimethylstannane.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.50 (1H, s) 7.40–7.29 (2H, m) 7.24–7.18 (2H, m) 7.07–7.01 (1H, m) 6.24–6.20 (1H, m) 5.73 (2H, s) 2.15–2.11 (4H, m) 2.61–2.54 (4H, m).

Example 74-(3-Chlorobenzyl)-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, steps (b) and (c) from 2-bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester see step (a), Example 5) and (5-methylthien-2-yl)trimethylstannane.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.61 (1H, s) 7.43 (1H, s) 7.34–7.31 (2H, m) 7.22–7.19 (2H, m) 7.13 (1H, d, *J* = 1.9 Hz) 7.05–7.02 (1H, m) 6.79 (1H, d, *J* = 1.9 Hz) 5.77 (2H, s) 2.45 (3H, s).

Example 84-(3-Chlorobenzyl)-2-(4-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, steps (b) and (c) from 2-bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester see step (a), Example 5) and trimethyl-(4-methylthien-2-yl)stannane.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.62 (1H, s) 7.49 (1H, s) 7.33–7.30 (2H, m) 7.22–7.02 (5H, m) 5.77 (2H, s) 2.20 (3H, s).

Example 94-(3-Bromobenzyl)-2-(4-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid(a) 2-Bromo-4-(3-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

5 The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1 (a)) and 3-bromobenzyl chloride.

(b) 4-(3-Bromobenzyl)-2-(4-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

10 A mixture of 2-bromo-4-(3-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (399 mg, 0.9 mmol; see step (a) above), tributyl-(4-methylthien-2-yl)stannane (852 mg, 2.2 mmol), Pd(PPh₃)₄ (60 mg, 0.052 mmol) and toluene (5 mL) was heated at reflux for 4 h, poured into Na₂CO₃ (aq, sat, 20 mL) and
15 extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (MgSO₄), concentrated and purified by chromatography, yielding the sub-title compound (269 mg, 65%).

(c) 4-(3-Bromobenzyl)-2-(4-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

20 The title compound was prepared in accordance with Example 5, step (c) from 4-(3-bromobenzyl)-2-(4-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above).

25 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.49-7.05 (8H, m) 5.77 (2H, s) 2.21 (3H, s).

Example 102-Phenylethynyl-4-(4-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid(a) 2-Bromo-4-(4-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

5 The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1 (a)) and 4-bromobenzyl chloride.

(b) 2-Phenylethynyl-4-(4-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester
10

A mixture of 2-bromo-4-(4-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (399 mg, 0.9 mmol; see step (a), Example 9), phenylethynyl trimethylstannane (583 mg, 2.2 mmol), Pd(PPh₃)₄ (60 mg, 0.052 mmol) and toluene (5 mL) was heated at reflux for 4 h under argon, poured into Na₂CO₃ (aq, 15 sat, 20 mL) and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (MgSO₄), concentrated and purified by chromatography, yielding the sub-title compound (297 mg, 68%).

(c) 2-Phenylethynyl-4-(4-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid
20

The title compound was prepared in accordance with Example 5, step (c) from 2-phenylethynyl-4-(4-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.64-7.42 (14H, m) 7.19 (1H, s) 7.15 (1H, s) 5.81 (2H, s).
25

Example 112-(5-Methylthien-2-yl)-4-[4-(5-methylthien-2-yl)benzyl]thieno[3,2-*b*]pyrrole-5-carboxylic acid

30 The title compound was prepared in accordance with Example 10, step (b) from 2-bromo-4-(4-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see

Example 10, step (a)) and (5-methylthien-2-yl)trimethylstannane, followed by hydrolysis in accordance with Example 5, step (c).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 12.58 (1H, br s) 7.52 (1H, s) 7.48 (1H, s) 7.39 (1H, s) 7.22 (1H, d, $J = 2.1$ Hz) 7.15-7.11 (4H, m) 6.79-6.78 (2H, m) 5.77 (2H, s) 2.44 (6H, s).

Example 12

2-Phenylethynyl-4-(3-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 10, step (b) from 2-bromo-4-(3-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 9, step (a)) and phenylethynyltrimethylstannane followed by hydrolysis in accordance with Example 5, step (c).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.67 (1H, s) 7.56-7.51 (4H, m) 7.43-7.35 (9H, m) 7.25 (1H, s) 7.18-7.14 (1H, m) 5.80 (2H, s).

Example 13

2-(5-Methylthien-2-yl)-4-[3-(5-methylthien-2-yl)benzyl]thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 10, step (b) from 2-bromo-4-(3-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 9, step (a)) and (5-methylthiophen-2-yl)trimethyl stannane, followed by hydrolysis in accordance with Example 5 step (c).

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 12.59 (1H, s) 7.48-7.41 (3H, m) 7.34-7.21 (3H, m) 7.12 (1H, d, $J = 3.3$ Hz) 6.95 (1H, d, $J = 7.7$ Hz) 6.82-6.78 (2H, m) 5.79 (2H, s) 2.45 (6H, s).

Example 142-Phenylethynyl-4-(2-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid(a) 2-Bromo-4-(2-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

- 5 The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1 (a)) and 2-bromobenzyl chloride.

(b) 2-Phenylethynyl-4-(2-phenylethynylbenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

10

The title compound was prepared in accordance with Example 10, step (b) from 2-bromo-4-(2-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (a) above) and phenylethynyltrimethylstannane, followed by hydrolysis in accordance with Example 5, step (c).

- 15 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.66-7.61 (3H, m) 7.46-7.44 (9H, m) 7.34-7.30 (3H, m) 6.46-6.42 (1H, m) 6.03 (2H, s).

Example 152-(5-Methylthien-2-yl)-4-[2-(5-methylthien-2-yl)benzyl]thieno[3,2-*b*]pyrrole-5-carboxylic acid

20

The title compound was prepared in accordance with Example 10, step (b) from 2-bromo-4-(2-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 14, step (a)) and (5-methylthiophen-2-yl)trimethylstannane, followed by hydrolysis in accordance with Example 5, step (c).

- 25 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.43 (1H, s) 7.40-7.37 (1H, m) 7.32-7.27 (1H, m) 7.24-7.21 (2H, m) 7.15-7.13 (2H, m) 7.10-7.08 (1H, m) 6.92 (1H, d, *J* = 2.6 Hz) 6.78 (1H, d, *J* = 2.6 Hz) 6.32 (1H, d, *J* = 7.0 Hz) 5.88 (2H, s) 2.50 (3H, s) 2.44 (3H, s).

Example 162-(4-Methylthien-2-yl)-4-[2-(4-methylthien-2-yl)benzyl]thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 10, step (b) from
5 2-bromo-4-(2-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 14, step (a)) and (4-methylthiophen-2-yl)trimethylstannane, followed by hydrolysis accordance with Example 5, step (c).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.46 (1H, s) 7.42-7.38 (1H, m) 7.32-7.18 (6H, m) 7.14-7.11 (2H, m) 6.33 (1H, m) 5.89 (2H, s) 2.30 (3H, s) 2.19 (3H, s).

Example 172-[3,5-Bis(trifluoromethyl)phenyl]-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

15 (a) 2-[3,5-Bis(trifluoromethyl)phenyl]-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A mixture of 2-bromo-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (400 mg, 1.0 mmol; see Example 5, step (a)), 3,5-bis(trifluoromethyl)-phenylboronic acid (567 mg, 2.2 mmol), K₃PO₄ (1.38 g, 6.5 mmol), Pd(OAc)₂ (22
20 mg, 0.098 mmol) and 2-di(*tert*-butyl)phosphinobiphenyl (60 mg, 0.20 mmol) in toluene (10 mL) was heated at reflux for 14 h under argon, poured into Na₂CO₃ (aq, 10%, 50 ml) and extracted with EtOAc. The combined extracts were dried (Na₂SO₄), concentrated and purified by chromatography, affording 362 mg (68%) of the sub-title product.

25 (b) 2-[3,5-Bis(trifluoromethyl)phenyl]-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (c) from
30 2-[3,5-bis(trifluoromethyl)phenyl]-4-(3-chlorobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (a) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 8.28-8.26 (3H, m) 8.03 (1H, s) 7.35-7.31 (3H, m) 7.20 (1H, s) 7.06-7.03 (1H, m) 5.79 (2H, s).

Example 184-Biphenyl-4-ylmethyl-2-phenylthieno[3,2-*b*]pyrrole-5-carboxylic acid5 (a) 4-Biphenyl-4-ylmethyl-2-phenylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A mixture of 2-bromo-4-(4-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (443 mg, 1.0 mmol; see Example 10, step (a)), phenylboronic acid (366 mg, 3.0 mmol), Pd(OAc)₂ (22.4 mg, 0.1 mmol), K₃PO₄ (1.49 g, 7.0 mmol), tri-*o*-tolylphosphine (65 mg, 0.2 mmol) and toluene (10 mL) was heated at reflux for 5 h under argon. The mixture was poured into NH₄Cl (aq, 10%, 50 mL) and extracted with EtOAc. The combined extracts were dried (Na₂SO₄), concentrated and purified by chromatography, affording 197 mg (45%) of the sub-title product.

15 (b) 4-Biphenyl-4-ylmethyl-2-phenylthieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (c) from 4-biphenyl-4-ylmethyl-2-phenylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (a) above).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.80 (1H, m) 7.71-7.58 (6H, m) 7.43-7.24 (9H, m) 5.85 (2H, s).

Example 194-(4'-Ethoxybiphenyl-3-ylmethyl)-2-(4-ethoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

25 The title compound was prepared in accordance with Example 18, step (a) from 2-bromo-4-(3-bromobenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 9, step (a)) and 4-ethoxyphenylboronic acid, followed by hydrolysis in accordance with Example 5, step (c).

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.57 (1H, s) 7.67-7.47 (7H, m) 7.37-7.30 (1H, m) 7.21 (1H, s) 7.02-6.96 (5H, m) 5.83 (2H, s) 4.06 (4H, q, *J* = 7.0 Hz) 1.33 (6H, t, *J* = 7.0 Hz).

Example 204-(3-Chlorobenzyl)-2-(4-isopropoxyphenyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid5 (a) 5-Bromo-4-methylthiophene-2-carboxaldehyde

n-BuLi (2.5 M in hexanes, 40 mL, 100 mmol) was added to 3-methylthiophene (9.7 mL, 100 mmol) in THF (100 mL) at -78 °C under argon. After 1 h, DMF (8.6 mL, 110 mmol) was added and the mixture was allowed to warm to rt. After 24 h at rt, HCl (aq, 1 M, 50 mL) was added and the mixture was extracted with Et₂O.

10 The combined extracts were washed with brine, dried (MgSO₄), concentrated and distilled to afford 4-methylthiophene-2-carboxaldehyde (11.4g, 90%), which was dissolved in a mixture of CHCl₃ (60 mL) and AcOH (60 mL). To the resulting solution, *N*-bromosuccinimide (16.0 g, 90 mmol) was added in portions. The mixture was stirred at rt for 12 h, poured into Na₂CO₃ (aq, 20%, 250 mL) and
15 extracted with CH₂Cl₂. The combined extracts were washed with brine, dried (MgSO₄), concentrated and recrystallised from hexanes with few drops of CH₂Cl₂ to yield the sub-title compound (15.1 g, 82%).

(b) 2-Bromo-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

20 The sub-title compound was prepared in accordance with Preparation 1 (a) from 5-bromo-4-methylthiophene-2-carboxaldehyde (see step (a) above) and azidoacetic acid ethyl ester.

25 (c) 2-Bromo-4-(3-chlorobenzyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromo-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above) and 3-chlorobenzyl chloride.

(d) 4-(3-Chlorobenzyl)-2-(4-isopropoxyphenyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (b) from 2-bromo-4-(3-chlorobenzyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (c) above) and (4-isopropoxyphenyl)trimethylstannane, followed by hydrolysis in accordance with Example 5, step (c).

¹H-NMR (200 MHz DMSO-*d*₆, ppm) δ 12.57 (1H, s) 7.39-7.30 (5H, m) 7.00-6.95 (3H, m) 6.85-6.82 (1H, m) 5.97 (2H, s) 4.64 (1H, m) 2.20 (3H, s) 1.27 (6H, d, *J* = 5.9 Hz).

Example 21

4-(3-Chlorobenzyl)-3-methyl-2-phenylethynylthieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (b) from 2-bromo-4-(3-chlorobenzyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 20, step (c)) and phenylethynyltrimethylstannane, followed by hydrolysis in accordance with Example 5, step (c).

¹H-NMR (200 MHz DMSO-*d*₆, ppm) δ 7.55-7.52 (2H, m) 7.43-7.33 (5H, m) 7.26 (1H, s) 6.89 (1H, s) 6.83-6.80 (1H, m) 5.99 (2H, s) 2.34 (3H, s).

Example 22

4-(3-Chlorobenzyl)-3-methyl-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (b) from 2-bromo-4-(3-chlorobenzyl)-3-methylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 20, step (c)) and (5-methylthiophen-2-yl)tributylstannane, followed by hydrolysis in accordance with Example 5, step (c).

¹H-NMR (200 MHz DMSO-*d*₆, ppm) δ 12.59 (1H, s) 7.39-7.25 (3H, m) 6.99-6.98 (2H, m) 6.83-6.81 (2H, m) 5.97 (2H, s) 2.44 (3H, s) 2.28 (3H, s).

Example 234-[3,5-Bis(trifluoromethyl)benzyl]-3,6-diphenylthieno[3,2-*b*]pyrrole-5-carboxylic acid5 (a) 4-[3,5-Bis(trifluoromethyl)benzyl]-3-bromo-6-iodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Preparation 1, steps (a-c) from 4-bromothiophene-2-carboxaldehyde and azidoacetic acid ethyl ester (step (a)), followed by iodination (step (b)) and *N*-alkylation with 1-bromomethyl-3,5-
10 bis(trifluoromethyl)benzene (step (c)).

(b) 4-[3,5-Bis(trifluoromethyl)benzyl]-3,6-diphenylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A mixture of 4-[3,5-bis(trifluoromethyl)benzyl]-3-bromo-6-iodothieno[3,2-*b*]-
15 pyrrole-5-carboxylic acid ethyl ester (300 mg, 0.48 mmol; see step (a) above), phenylboronic acid (175 mg, 1.44 mmol), K₃PO₄ (713 mg, 3.36 mmol), Pd(OAc)₂ (5 mg, 0.024 mmol), tri-*o*-tolylphosphine (15 mg, 0.048 mmol) and toluene (10 mL) was stirred under argon at rt for 30 min and at 100°C for 2 h. The mixture was cooled to rt and poured into NaHCO₃ (aq, sat) and extracted with EtOAc. The
20 combined extracts were washed with H₂O and brine, dried (Na₂SO₄), concentrated and purified by chromatography affording the sub-title compound (130 g, 47%).

(c) 4-[3,5-Bis(trifluoromethyl)benzyl]-3,6-diphenylthieno[3,2-*b*]pyrrole-5-carboxylic acid

25 The title compound was prepared in accordance with Preparation 1, step (d) from 4-[3,5-bis(trifluoromethyl)benzyl]-3,6-diphenylthieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester.

¹H NMR (acetone-*d*₆, 200 MHz) δ 11.2 (1H, br s) 7.83 (1H, s) 7.70-7.62 (2H, m) 7.53-7.25 (9H, m) 7.23 (2H, s) 5.84 (2H, s).

Example 24

4-[3,5-Bis(trifluoromethyl)benzyl]-3-(4-*tert*-butylphenyl)-2,6-diiodothieno[3,2-*b*]-pyrrole-5-carboxylic acid

5 (a) 3-(4-*tert*-Butylphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

A mixture of 3-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (617 mg, 2.25 mmol (see Preparation 1 (a)), 4-*tert*-butylphenylboronic acid (601 mg, 3.38 mmol), K₃PO₄ (1.44 g, 6.76 mmol), Pd(OAc)₂ (49 mg, 0.23 mmol), 2,2'-bis(di-*tert*-butylphosphino)-1,1'-biphenyl (137 mg, 0.46 mmol) and toluene (15 mL) was
 10 stirred under argon at rt for 30 min, and at 100°C for 1 h. The mixture was cooled to rt, poured into NaHCO₃ (aq, sat) and extracted with EtOAc. The combined extracts were washed with H₂O and brine, dried (Na₂SO₄), concentrated and purified by chromatography affording the sub-title compound (592 mg, 80%).

15 (b) 3-(4-*tert*-Butylphenyl)-2,6-diiodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Preparation 1, step (b) from NaI (648 mg, 4.32 mmol), *N*-chlorosuccinimide (576 mg, 4.32 mmol) and 3-(4-*tert*-butylphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (590 mg,
 20 1.80 mmol). Yield 829 mg (80%).

(c) 4-[3,5-Bis(trifluoromethyl)benzyl]-3-(4-*tert*-butylphenyl)-2,6-diiodothieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Preparation 1, steps (c) and
 25 (d) from 3-(4-*tert*-butylphenyl)-2,6-diiodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above) and 1-bromomethyl-3,5-bis(trifluoromethyl)-benzene.

¹H NMR (DMSO-*d*₆, 200 MHz) δ13.5-13.1 (1H, br s) 7.91 (1H, s) 7.28-7.21 (2H, m) 7.04 (2H, s) 6.94-6.88 (2H, m) 5.45 (2H, s) 1.23 (9H, s).

Example 253-(4-*tert*-Butylphenyl)-2,6-diiodo-4-(3-phenoxybenzyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Preparation 1, steps (c) and
5 (d) from 3-(4-*tert*-butylphenyl)-2,6-diiodothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester and 3-phenoxybenzylbromide.

¹H NMR (DMSO-*d*₆, 200 MHz) δ 13.4-13.0 (1H, br s) 7.38-7.28 (4H, m) 7.14-7.05 (2H, m) 6.99-6.93 (2H, m) 6.88-6.81 (2H, m) 6.72 (1H, dd, *J* = 8.2, 2.2 Hz) 6.13 (1H, d, *J* = 7.8 Hz) 5.94-5.91 (1H, m) 5.34 (2H, s) 1.27 (9H, s).

10

Example 262,4-Bis-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid(a) 2-(4-Isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

15 The sub-title compound was prepared in accordance with Example 5, step (b) from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1, step (a)) and (4-isopropoxyphenyl)trimethylstannane.

20 (b) 2,4-Bis-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

An oven dried ACE[®] pressure tube was charged with 2-(4-isopropoxyphenyl)-thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (165 mg, 0.5 mmol; see step (a) above), K₃PO₄ (223 mg, 1.05 mmol), 4-isopropoxyphenylbromide (130 mg, 0.6 mmol) and toluene (1.0 mL) and flushed with argon. A solution of CuI (22.9 mg, 0.12 mmol) and *N,N*-dimethyl-1,2-diaminoethane (26 μL, 0.24 mmol) in toluene
25 (1.0 mL) was added. The mixture was heated at 90°C for 36 h, cooled, filtered through Celite[®] and the solids were washed with EtOAc. The combined liquids were washed with NH₄OH (aq, sat) and brine, dried (Na₂SO₄), concentrated and purified by chromatography affording the sub-title compound (190 mg, 82%).

30

(c) 2,4-Bis-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (c) from 2,4-bis-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above).

- 5 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 13.0-11.5 (1H, br s) 7.58-7.51 (2H, m) 7.32-7.25 (2H, m) 7.24 (1H, s) 7.04 (1H, s) 7.00-6.93 (2H, m) 6.93-6.86 (2H, m) 4.64 (1H, m) 4.61 (1H, m) 1.30 (6H, d, *J* = 6.1 Hz) 1.24 (6H, d, *J* = 6.1 Hz).

Example 27

- 10 2-(4-Isopropoxyphenyl)-4-(6-isopropoxypyridin-3-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 26, step (a)) and 5-bromo-2-isopropoxypyridine, followed by hydrolysis.

- 15 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.5-12.4 (1H, br s) 8.24 (1H, d, *J* = 2.7 Hz) 7.77 (1H, dd, *J* = 8.8, 2.7 Hz) 7.63-7.56 (2H, m) 7.34 (1H, s) 7.18 (1H, s) 6.96-6.90 (2H, m) 6.86 (1H, d, *J* = 8.8 Hz) 5.31 (1H, m) 4.64 (1H, septet, *J* = 6.1 Hz) 1.35 (6H, d, *J* = 6.2 Hz) 1.26 (6H, d, *J* = 6.1 Hz).

20 Example 28

2-(4-Isopropoxyphenyl)-4-(4-methyl-3-nitrophenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example

- 25 26, step (a)) and 4-bromo-1-methyl-2-nitrobenzene, followed by hydrolysis.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.55 (1H, s) 8.06 (1H, d, *J* = 2.1 Hz) 7.73 (1H, dd, *J* = 8.2, 2.1 Hz) 7.63-7.53 (3H, m) 7.37 (1H, s) 7.24 (1H, s) 6.95-6.87 (2H, m) 4.62 (1H, m) 2.59 (3H, s) 1.24 (6H, d, *J* = 6.0 Hz).

Example 294-[4-(2-Carboxyvinyl)phenyl]-2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 26, step (a)) and 3-(4-bromophenyl)acrylic acid ethyl ester, followed by hydrolysis.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 12.55-12.40 (2H, br s) 7.84-7.77 (2H, m) 7.68 (1H, d, *J* = 16.0 Hz) 7.61-7.54 (2H, m) 7.50-7.43 (2H, m) 7.34 (1H, s) 7.16 (1H, s) 6.95-6.88 (2H, m) 6.59 (1H, d, *J* = 16.0 Hz) 4.62 (1H, m) 1.24 (6H, d, *J* = 6.0 Hz).

Example 304-(4-Cyclopentyloxyphenyl)-2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 26, step (a)) and 1-bromo-4-cyclopentyloxybenzene, followed by hydrolysis.

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.56-7.49 (2H, m) 7.26-7.19 (2H, m) 7.02 (1H, s) 6.96 (1H, s) 6.93-6.88 (4H, m) 4.86-4.78 (1H, m) 4.62 (1H, m) 1.96-1.60 (8H, m) 1.26 (6H, d, *J* = 6.0 Hz).

Example 314-[4-(1-Carboxy-1-methylethoxy)phenyl]-2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 26, step (a)) and 2-(4-bromophenoxy)-2-methylpropionic acid ethyl ester (prepared as described in *J. Am. Chem. Soc.*, 77, 6644 (1955), followed by hydrolysis.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 13.1-12.4 (2H, br s) 7.60-7.55 (2H, m) 7.36-7.30 (2H, m) 7.30 (1H, s) 7.07 (1H, s) 6.94-6.88 (4H, m) 4.63 (1H, m) 1.58 (6H, s) 1.26 (6H, d, $J = 6.0$ Hz).

5 Example 32

2-(4-Isopropoxyphenyl)-4-(5'-methyl-2,2'-bithienyl-5-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

(a) 5-Bromo-5'-methyl-2,2'-bithienyl

10 A mixture of 5-methyl-2-thienylmagnesium bromide (prepared from 2-bromo-5-methylthiophene (1.77 g, 10 mmol) and Mg (0.24 g, 10 mmol) in THF (50 mL)), 2-bromothiophene (0.86g, 10 mmol), bis(diphenylphosphino)propane nickel dichloride (54 mg, 0.1 mmol) and THF (20 mL) was stirred at rt for 2 h and at
15 reflux for 4 h. The mixture was poured into NH_4Cl (aq, sat, 100 mL) and extracted with Et_2O . The combined extracts were washed with brine, dried (MgSO_4), concentrated and distilled under reduced pressure affording 1.53 g (85%) of 5-methyl-[2,2']bithiophene, which was dissolved in CHCl_3 (25 mL) and AcOH (25 mL). To this solution was added *N*-bromosuccinimide (1.6g, 9.0 mmol) in
20 portions over 1 h. The mixture was stirred at rt for 24 h, poured into Na_2CO_3 (aq, sat, 100 mL) and extracted with CH_2Cl_2 . The combined extracts were washed with brine, dried (MgSO_4), concentrated and crystallised from petroleum ether affording the sub-title compound (1.98 g, 90%).

25 (b) 2-(4-Isopropoxyphenyl)-4-(5'-methyl-2,2'-bithienyl-5-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 26 from 2-(4-isopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 26, step (a)) and 5-bromo-5'-methyl-[2,2']bithiophenyl (see step (a) above), followed by hydrolysis.

30 200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 7.60-7.53 (2H, m) 7.18 (1H, s) 7.11-7.05 (4H, m) 6.93-6.86 (2H, m) 6.78 (1H, dd, $J = 3.4, 1.1$ Hz) 4.62 (1H, m) 2.45 (3H, s) 1.25 (6H, d, $J = 6.0$ Hz).

Example 334-(4-Cyclopentyloxyphenyl)-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

5

(a) 2-Bromo-4-(4-cyclopentyloxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

Anhydrous CH₂Cl₂ (10 mL), Et₃N (340 μL, 2.43 mmol), pyridine (200 μL, 2.43 mmol) and 3Å molecular sieves (*ca.* 1.0 g) were added to 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (332 mg, 1.21 mmol; see Example 1 step 10 (a)), Cu(OAc)₂ (440 mg, 2.43 mmol), and 4-cyclopentyloxyphenylboronic acid (500 mg, 2.43 mmol). The mixture was stirred vigorously at rt for 36 h and filtered through Celite[®]. The solids were washed with EtOAc, and the combined liquids concentrated and purified by chromatography to afford the sub-title compound (356 mg, 72%).

15

(b) 4-(4-Cyclopentyloxyphenyl)-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

2-Bromo-4-(4-cyclopentyloxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (248 mg, 0.57 mmol), (5-methylthiophen-2-yl)tributylstannane (232 mg, 0.6 mmol) and Pd(PPh₃)₄ (60 mg, 0.052 mmol) were dissolved in toluene (3 mL) and heated at reflux for 3 h. The mixture was poured into NH₄Cl (aq, sat, 20 mL) and extracted with EtOAc. The combined extracts were washed with brine, dried (MgSO₄), concentrated and purified by chromatography affording the sub-title compound (196 mg, 76%).

25

(c) 4-(4-Cyclopentyloxyphenyl)-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (c) from 4-(4-cyclopentyloxyphenyl)-2-(5-methylthien-2-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above).

30

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 12.35 (1H, s) 7.32-7.28 (2H, m) 7.28 (1H, s) 7.16 (1H, d, $J = 3.66$ Hz) 7.00-6.96 (2H, m) 6.84 (1H, s) 6.77 (1H, d, $J = 3.66$ Hz) 4.90-4.82 (1H, m) 2.43 (3H, s) 1.98-1.62 (8H, m).

5 Example 34

4-(4-Isopropoxyphenyl)-2-(5-methylthien-2-yl)thieno[3.2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 33 from 2-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1 (a)),
10 4-isopropoxyphenylboronic acid and (5-methylthien-2-yl)tributylstannane, followed by hydrolysis.

200 MHz ^1H -NMR (DMSO- d_6 , ppm) δ 12.40-12.30 (1H, br s) 7.32-7.28 (3H, m) 7.17 (1H, d, $J = 3.7$ Hz) 7.02-6.97 (2H, m) 6.85 (1H, s) 6.77 (1H, d, $J = 3.7$ Hz) 4.73-4.61 (1H, m) 2.43 (3H, s) 1.32 (6H, d, $J = 6.4$ Hz).

15

Example 35

6-(3-Chlorobenzyl)-2-(4-isopropoxyphenyl)-6H-thieno[2,3-*b*]pyrrole-5-carboxylic acid

20 (a) 5-Bromothiophene-3-carboxaldehyde

AlCl_3 (15g, 0.112 mol) was added in portions over 2 h to a solution of thiophene-3-carboxaldehyde (5g, 0.044 mol) in CH_2Cl_2 (150 mL) at rt. Br_2 (2.13 mL, 0.041 mol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was heated at reflux for 6 h, cooled, poured into H_2O (250 mL) and extracted with CH_2Cl_2 . The
25 combined extracts were washed with brine, dried (MgSO_4), concentrated and distilled to yield the sub-title compound 5.4 g (64%).

(b) 2-Bromothieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Preparation 1, step (a)
30 from 5-bromothiophene-3-carboxaldehyde (see step (a) above) and azidoacetic acid ethyl ester.

(c) 2-Bromo-6-(3-chlorobenzyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 1, step (a) from 2-bromothieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (b) above) and 3-chlorobenzyl bromide.

5

(d) 6-(3-Chlorobenzyl)-2-(4-isopropoxyphenyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester

The sub-title compound was prepared in accordance with Example 5, step (b) from 2-bromo-6-(3-chlorobenzyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (c) above) and (4-isopropoxyphenyl)trimethylstannane.

10

(e) 6-(3-Chlorobenzyl)-2-(4-isopropoxyphenyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 5, step (c) from 6-(3-chlorobenzyl)-2-(4-isopropoxyphenyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (see step (d) above).

15

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.50-7.46 (2H, m) 7.40-7.35 (3H, m) 7.25 (1H, s) 7.16-7.12 (2H, m) 6.95-6.91 (2H, m) 5.72 (2H, s) 4.68-4.56 (1H, m) 1.25 (6H, d, *J* = 6.4 Hz).

20

Example 36

6-(3-Chlorobenzyl)-2-(5-methylthien-2-yl)thieno[2,3-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 35 from 2-bromo-6-(3-chlorobenzyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 35, step (c)) and (5-methylthiophen-2-yl)tributylstannane, followed by hydrolysis.

25

200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.39-7.37 (2H, m) 7.25 (1H, s) 7.16-7.10 (3H, m) 7.00 (1H, d, *J* = 3.4 Hz) 6.74 (1H, d, *J* = 3.4 Hz) 5.72 (2H, s) 2.43 (3H, s).

Example 376-(3-Chlorobenzyl)-2-(4-methylthien-2-yl)thieno[2,3-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Example 35 from 2-bromo-6-(3-chlorobenzyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid ethyl ester (see Example 5, step (c)) and (4-methylthiophen-2-yl)tributylstannane, followed by hydrolysis. 200 MHz ¹H-NMR (DMSO-*d*₆, ppm) δ 7.39-7.36 (2H, m) 7.26 (1H, s) 7.23 (1H, s) 7.16-7.12 (2H, m) 7.07-7.04 (2H, m) 5.72 (2H, s) 2.18 (3H, s).

Example 38

10 4-[3,5-Bis(trifluoromethyl)benzyl]-3-(2-oxopyrrolidin-1-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

(a) 4-[3,5-Bis(trifluoromethyl)benzyl]-3-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester

15 The sub-title compound was prepared in accordance with Preparation 1, step (c) from 3-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (see Preparation 1, step (a)) and 1-bromomethyl-3,5-bis(trifluoromethyl)benzene.

20 (b) 4-[3,5-Bis(trifluoromethyl)benzyl]-3-(2-oxopyrrolidin-1-yl)thieno-[3,2-*b*]-pyrrole-5-carboxylic acid ethyl ester

2-Pyrrolidinone (82 μL, 0.54 mmol) and MeNHCH₂CH₂NHMe (28 μL, 0.27 mmol) were added to a mixture of 4-[3,5-bis(trifluoromethyl)benzyl]-3-bromothieno[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester (450 mg, 0.90 mmol; see step (a) above), K₃PO₄ (400 mg, 1.88 mmol), CuI (8.6 mg, 0.45 mmol) and toluene (5 mL). The mixture was stirred at 110°C for 48 h, cooled to rt and filtered through Celite[®]. The solids were washed with EtOAc and the combined liquids were concentrated and purified by chromatography to yield the sub-title compound (171 mg, 38%).

(c) 4-[3,5-Bis(trifluoromethyl)benzyl]-3-(2-oxopyrrolidin-1-yl)thieno[3,2-*b*]pyrrole-5-carboxylic acid

The title compound was prepared in accordance with Preparation 1, step (d) from 4-[3,5-bis(trifluoromethyl)benzyl]-3-(2-oxopyrrolidin-1-yl)thieno-[3,2-*b*]pyrrole-5-carboxylic acid ethyl ester.

¹H NMR (DMSO-*d*₆, 200 MHz) δ 12.86 (1H, s) 8.01 (1H, s) 7.55-7.52 (3H, m) 7.36 (1H, s) 5.87 (2H, s) 3.35-3.23 (2H, m) 2.30 (2H, t, *J* = 8.0 Hz) 1.89-1.71 (2H, m).

10 Example 39

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

2,6-bis-(4-isopropoxyphenyl)thieno[2,3-*b*]pyrrole-5-carboxylic acid;

6-(4-isopropoxyphenyl)-2-(5-methylthien-2-yl)thieno[2,3-*b*]pyrrole-5-carboxylic acid;

6-(4-isopropoxyphenyl)-2-(4-methylthien-2-yl)thieno[2,3-*b*]pyrrole-5-carboxylic acid;

4-(4-cyclopentyloxyphenyl)-2-(4-cyclopropoxyphenyl)thieno[3,2-*b*]pyrrole-5-carboxylic acid; and

4-(4-(cyclopentyloxy)phenyl)-2-(4-cyclopropoxyphenyl)thien[3,2-*b*]pyrrole-5-carboxylic acid.

Example 40

Title compounds of the examples were tested in the biological test described above and were found to exhibit 50% inhibition of mPGES-1 at a concentration of 10 μM or below. For example, the following representative compounds of the examples exhibited the following IC₅₀ values:

Example 1: 390 nM

Example 2: 390 nM

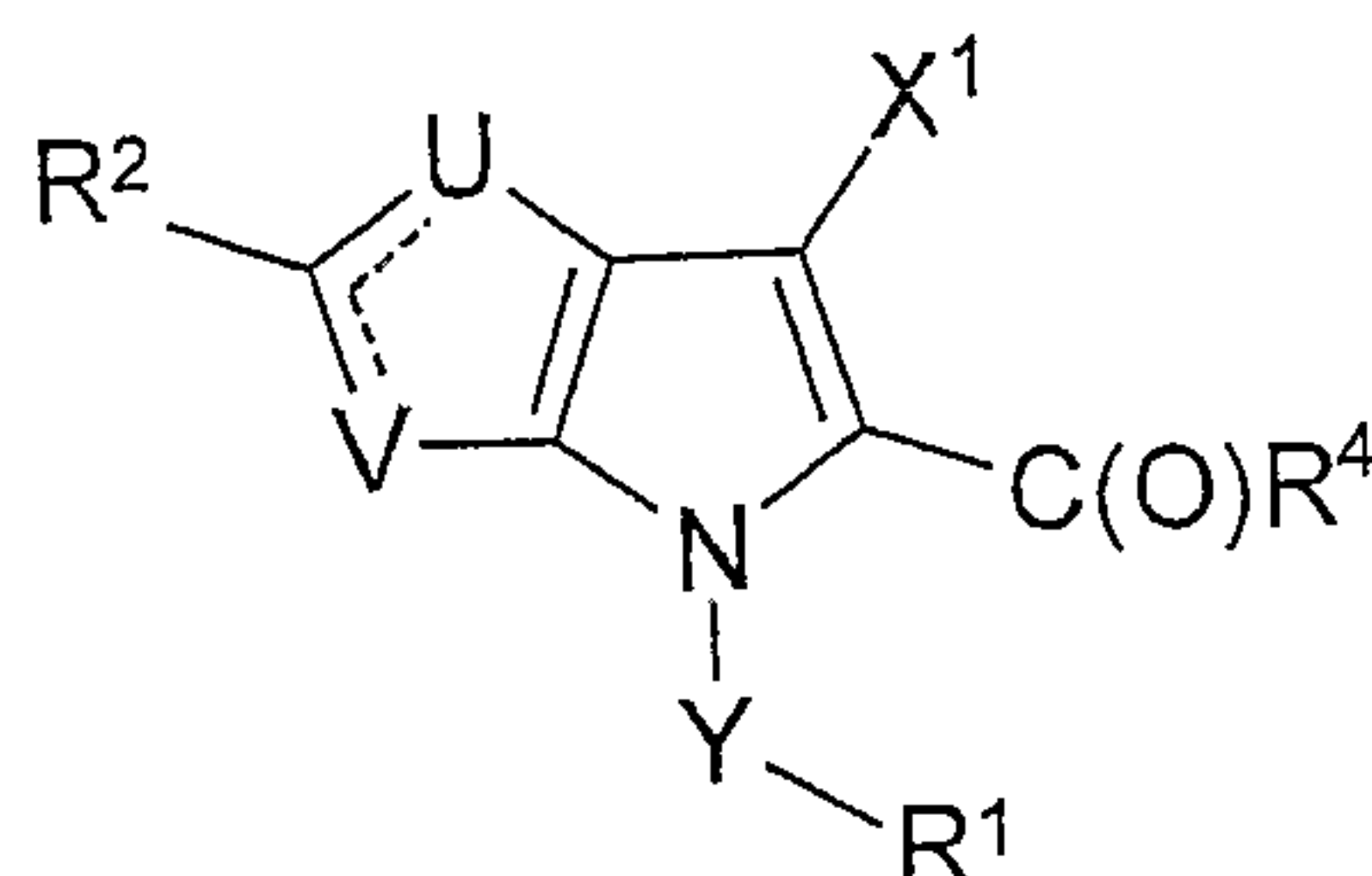
Example 4: 1300 nM

Example 28: 5100 nM

Example 35: 4700 nM

Claims

1. A compound of formula I,



I

wherein

one of U and V represents -S- and the other represents -C(R³)-;

when U represents -S-, the dotted line between the carbon atom bearing R² and V is a double bond and that between the carbon atom bearing R² and U is a single bond, and when V represents -S-, the dotted line between the carbon atom bearing R² and U is a double bond and that between the carbon atom bearing R² and V is a single bond;

one of the groups R² and R³ represents -D-E and the other represents H, halo, -NO₂, cyano or C₁₋₆ alkyl, which alkyl group is optionally substituted by one or more substituents selected from halo, hydroxy and C₁₋₆ alkoxy;

D represents a single bond, -O-, -C(R⁶)(R⁷)-, C₂₋₄ alkylene, -C(O)- or -S(O)_m-;

R¹ represents an aryl group or a heteroaryl group, both of which groups are optionally substituted by one or more substituents selected from A;

E represents either an aryl or heteroaryl group (both of which groups are optionally substituted by one or more substituents selected from A), or a

heterocycloalkyl group (which group is optionally substituted by one or more substituents selected from G^1 and/or Z^1);

5 R^6 and R^7 independently represent H, halo or C_{1-6} alkyl, which latter group is optionally substituted by halo, or R^6 and R^7 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;

10

X^1 represents H, halo, $-N(R^8)-J-R^9$ or $-Q-X^2$;

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

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

m represents 0, 1 or 2;

X^2 represents:

20 (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 ;

25 Y represents a single bond, or a C_{1-8} alkylene or C_{2-8} heteroalkylene chain, both of which latter two groups:

(i) optionally contain one or more unsaturations;

(ii) are optionally substituted by one or more substituents selected from halo, $-R^{10a}$, $-N(R^{10b})R^{11b}$, $-OR^{10c}$ and $=O$; and/or

30 (iii) may comprise an additional 3- to 8-membered ring formed between any one or more members of the C_{1-8} alkylene or C_{2-8} heteroalkylene chain, which ring optionally contains 1 to 3 heteroatoms and/or 1 to 3 unsaturations and which ring

is itself optionally substituted by one or more substituents selected from halo, $-R^{10d}$, $-N(R^{10e})R^{11e}$, $-OR^{10f}$ and $=O$;

R^4 represents $-OR^{12a}$ or $-N(R^{12b})R^{13b}$;

5

R^8 , R^9 , R^{10a} to R^{10f} , R^{11b} , R^{11e} , R^{12a} , R^{12b} and R^{13b} 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;

10 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^8 and R^9 , R^{10b} and R^{11b} , R^{10e} and R^{11e} , and R^{12b} and R^{13b} , may be linked together to form, along with the N atom and (in the case of R^9) the J group to which they are 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:

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 halo, cyano, $-N_3$, $-NO_2$, $-ONO_2$ or $-A^1-R^{14a}$;

wherein A^1 represents a single bond or a spacer group selected from $-C(O)A^2-$, $-S(O)_2A^3-$, $-N(R^{15a})A^4-$ or $-OA^5-$, in which:

A^2 represents a single bond, $-O-$, $-N(R^{15b})-$ or $-C(O)-$;

A^3 represents a single bond, $-O-$ or $-N(R^{15c})-$;

30 A^4 and A^5 independently represent a single bond, $-C(O)-$, $-C(O)N(R^{15d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{15e})-$;

Z^1 represents =O, =S, =NOR^{14b}, =NS(O)₂N(R^{15f})R^{14c}, =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;

- 10 G² represents halo, cyano, -N₃, -NO₂, -ONO₂ or -A⁶-R^{16a};
 wherein A⁶ represents a single bond or a spacer group selected from -C(O)A⁷-, -S(O)₂A⁸-, -N(R^{17a})A⁹- or -OA¹⁰-, in which:
 A⁷ represents a single bond, -O-, -N(R^{17b})- or -C(O)-;
 A⁸ represents a single bond, -O- or -N(R^{17c})-;
 15 A⁹ and A¹⁰ independently represent a single bond, -C(O)-, -C(O)N(R^{17d})-, -C(O)O-, -S(O)₂- or -S(O)₂N(R^{17e})-;

Z^2 represents =O, =S, =NOR^{16b}, =NS(O)₂N(R^{17f})R^{16c}, =NCN or =C(H)NO₂;

- 20 R^{14a}, R^{14b}, R^{14c}, R^{15a}, R^{15b}, R^{15c}, R^{15d}, R^{15e}, R^{15f}, R^{16a}, R^{16b}, R^{16c}, R^{17a}, R^{17b}, R^{17c}, R^{17d}, R^{17e} and R^{17f} 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 G³;
 - 25 iii) C₁₋₈ alkyl or a heterocycloalkyl group, both of which are optionally substituted by one or more substituents selected from G³ and/or Z³; or
- any pair of R^{14a} to R^{14c} and R^{15a} to R^{15f}, and/or R^{16a} to R^{16c} and R^{17a} to R^{17f}, may be linked together to form 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
- 30 by one or more substituents selected from G³ and/or Z³;

G³ represents halo, cyano, -N₃, -NO₂, -ONO₂ or -A¹¹-R^{18a};

wherein A^{11} represents a single bond or a spacer group selected from $-C(O)A^{12}-$, $-S(O)_2A^{13}-$, $-N(R^{19a})A^{14}-$ or $-OA^{15}-$, in which:

A^{12} represents a single bond, $-O-$, $-N(R^{19b})-$ or $-C(O)-$;

A^{13} represents a single bond, $-O-$ or $-N(R^{19c})-$;

5 A^{14} and A^{15} independently represent a single bond, $-C(O)-$, $-C(O)N(R^{19d})-$, $-C(O)O-$, $-S(O)_2-$ or $-S(O)_2N(R^{19e})-$;

Z^3 represents $=O$, $=S$, $=NOR^{18b}$, $=NS(O)_2N(R^{19f})R^{18c}$, $=NCN$ or $=C(H)NO_2$;

10 R^{18a} , R^{18b} , R^{18c} , R^{19a} , R^{19b} , R^{19c} , R^{19d} , R^{19e} and R^{19f} 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,

15 $-N(R^{20a})R^{21a}$, $-OR^{20b}$ and $=O$; and

iii) an aryl or heteroaryl group, both of which are optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{20c})R^{21b}$ and $-OR^{20d}$; or any pair of R^{18a} to R^{18c} and R^{19a} to R^{19f} may be linked together to form a further 3-

20 to 8-membered ring, optionally containing 1 to 3 heteroatoms and/or 1 to 3 double bonds, which ring is optionally substituted by one or more substituents selected from halo, C_{1-4} alkyl, $-N(R^{20e})R^{21c}$, $-OR^{20f}$ and $=O$;

25 R^{20a} , R^{20b} , R^{20c} , R^{20d} , R^{20e} , R^{20f} , R^{21a} , R^{21b} and R^{21c} are independently selected from hydrogen and C_{1-4} alkyl, which latter group is optionally substituted by one or more halo groups;

or a pharmaceutically-acceptable salt thereof,

provided that, when R^2 represents $-D-E$ and:

30 (a) V represents S , D represents $-C(O)-$, E represents phenyl, X^1 represents $-Q-X^2$, Q represents a single bond, R^3 and X^2 both represent methyl, R^4 represents

ethoxy and Y represents a single bond, then R¹ does not represent an unsubstituted phenyl group; and

(b) when U represents S, D represents a single bond, E represents thien-2-yl or 3-aminophenyl, X¹ and R³ both represent H, R⁴ represents -OH or ethoxy and Y represents -CH₂-, then R¹ does not represent 3,4-dichlorophenyl.

2. A compound as claimed in Claim 1, wherein X¹ represents H, halo or -Q-X².
- 10 3. A compound as claimed in Claim 1 or Claim 2, wherein Q represents a single bond.
- 15 4. A compound as claimed in any one of the preceding claims, wherein X² represents an aryl group or a heteroaryl group, both of which are optionally substituted with one or more A groups, or an optionally unsaturated C₁₋₃ alkyl group optionally substituted with one or more G¹ groups.
- 20 5. A compound as claimed in any one of the preceding claims, wherein A represents G¹; a phenyl group, a thienyl group, both of which are optionally substituted by one or more B groups; or a methyl, ethyl, ethenyl, ethynyl or *t*-butyl group, each of which is optionally substituted by one or more G¹ groups.
- 25 6. A compound as claimed in any one of the preceding claims, wherein Y represents a single bond or a C₁₋₃ alkylene spacer group.
7. A compound as claimed in Claim 6, wherein Y represents a single bond.
8. A compound as claimed in any one of the preceding claims, wherein G¹ represents halo, -NO₂ or -A¹-R^{14a}.
- 30 9. A compound as claimed in any one of the preceding claims, wherein A¹ represents a single bond, -C(O)O-, -N(R^{15a})A⁴- or -OA⁵-.

10. A compound as claimed in any one of the preceding claims, wherein A⁴ and A⁵ independently represent a single bond.

5 11. A compound as claimed in any one of the preceding claims, wherein R^{14a} to R^{14c} independently represent H, a phenyl group, a heteroaryl group, a linear C₁₋₆ alkyl group, an unsaturated C₂₋₆ alkyl group, a branched C₂₋₆ alkyl group, or a cyclic C₃₋₆ alkyl group, which latter six groups are optionally substituted with one or more G³ substituents.

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12. A compound as claimed in any one of the preceding claims, wherein B represents methyl or G².

13. A compound as claimed in any one of the preceding claims, wherein G²
15 represents -OR^{16a}.

14. A compound as claimed in any one of the preceding claims, wherein R^{16a} to R^{16c} independently represent methyl or ethyl.

20 15. A compound as claimed in any one of the preceding claims, wherein G³ represents fluoro or -C(O)OH.

16. A compound as claimed in any one of the preceding claims, wherein the R² or R³ group that does not represent -D-E represents H, halo or C₁₋₃ alkyl.

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17. A compound as claimed in any one of the preceding claims, wherein D represents -C(R⁶)R⁷-, a single bond or a C₁₋₃ alkylene linker group.

18. A compound as claimed in any one of the preceding claims, wherein R^{12a}
30 and R^{12b} independently represent H or C₁₋₃ alkyl.

19. A compound as claimed in any one of the preceding claims, wherein, when R^4 represents $-N(R^{12b})R^{13b}$, R^{12b} represents H and R^{13b} represents a C_{1-4} alkyl group substituted by G^1 .

5 20. A compound as claimed in any one of the preceding claims, wherein, when R^4 represents $-OR^{12a}$, R^{12a} represents H.

21. A compound as claimed in any one of the preceding claims, wherein R^1 , X^2 (when X^2 represents an aryl or heteroaryl group) and/or E represent optionally substituted phenyl, naphthyl, pyrrolyl, furanyl, thienyl, pyrazolyl, 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, pyridazinyl, pyrimidinyl, pyrazinyl, indazolyl, benzimidazolyl, quinazolinyl, quinoxaliny, 1,3-benzodioxolyl, tetrazolyl, benzothiazolyl, and/or benzodioxanyl, groups.

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22. A compound as claimed in Claim 21, wherein E and R^1 independently represent optionally substituted pyridyl, phenyl, thienyl or imidazolyl.

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23. A compound as claimed in Claim 21 or Claim 22, wherein the optional substituents are selected from halo, cyano, $-NO_2$, C_{1-6} alkyl (which alkyl group may be linear, branched, cyclic, part-cyclic, unsaturated and/or optionally substituted with one or more $-CO_2H$ groups, one or more halo group or one or more phenyl groups), aryl (optionally substituted by one or more halo or C_{1-4} alkoxy group), heteroaryl (optionally substituted by one or more halo or C_{1-3} alkyl group), heterocycloalkyl (which heterocycloalkyl group is optionally substituted by one or more substituents selected from C_{1-3} alkyl and $=O$), $-OR^{22}$ and $-N(R^{22})R^{23}$, wherein R^{22} and R^{23} independently represent, H, phenyl or C_{1-6} alkyl (which alkyl groups are optionally substituted by one or more $-CO_2H$ groups or one or more halo groups).

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24. A compound as defined in any one of Claims 1 to 23, but without proviso (a), or a pharmaceutically-acceptable salt thereof, for use as a pharmaceutical.

25. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 23, but without proviso (a), or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

26. The use of a compound as defined in any one of Claims 1 to 23, but without proviso (a), or a pharmaceutically-acceptable salt thereof, for the manufacture of a medicament for the treatment of a disease in which inhibition of the activity of a member of the MAPEG family is desired and/or required.

27. A use as claimed in Claim 26, wherein the member of the MAPEG family is microsomal prostaglandin E synthase-1, leukotriene C₄ and/or 5-lipoxygenase-activating protein.

28. A use as claimed in Claim 27, wherein the member of the MAPEG family is microsomal prostaglandin E synthase-1.

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29. A use as claimed in any one of Claims 26 to 28, wherein the disease is inflammation.

30. A use as claimed in any one of Claims 26 to 29, wherein the disease is asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, inflammatory 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,

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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, 5 Paget's disease or a periodontal disease.

31. 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 10 defined in any one of Claims 1 to 23, but without the proviso (a), or a pharmaceutically-acceptable salt thereof, to a patient suffering from, or susceptible to, such a condition.

32. A method as claimed in Claim 31, wherein the member of the MAPEG 15 family is microsomal prostaglandin E synthase-1, leukotriene C₄ and/or 5-lipoxygenase-activating protein.

33. A method as claimed in Claim 32, wherein the member of the MAPEG family is microsomal prostaglandin E synthase-1.

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34. A combination product comprising:

(A) a compound as defined in any one of Claims 1 to 23, but without the provisos, or a pharmaceutically-acceptable salt thereof; and

(B) another therapeutic agent that is useful in the treatment of inflammation,

25 wherein each of components (A) and (B) is formulated in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

35. A combination product as claimed in Claim 34 which comprises a pharmaceutical formulation including a compound as defined in any one of 30 Claims 1 to 23, but without the provisos, or a pharmaceutically-acceptable salt thereof, another therapeutic agent that is useful in the treatment of inflammation, and a pharmaceutically-acceptable adjuvant, diluent or carrier.

36. A combination product as claimed in Claim 34 which comprises a kit of parts comprising components:

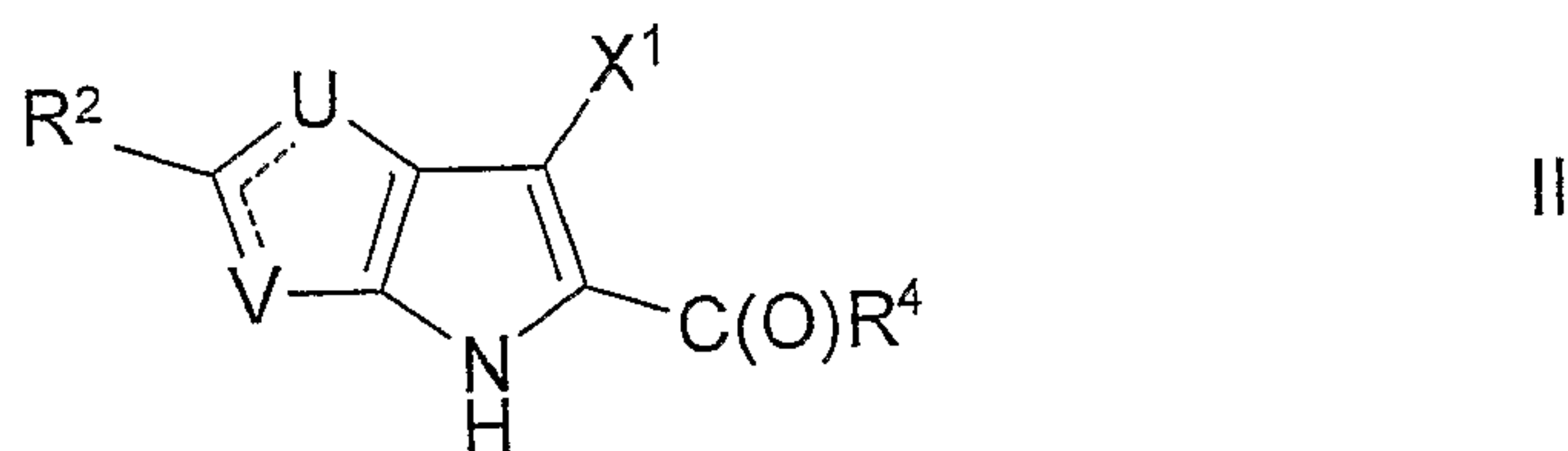
(a) a pharmaceutical formulation including a compound as defined in any one of Claims 1 to 23, but without the provisos, or a pharmaceutically-acceptable salt thereof, in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier; and

(b) a pharmaceutical formulation including another therapeutic agent that is useful in the treatment of inflammation in admixture with a 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.

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

(i) reaction of a compound of formula II,

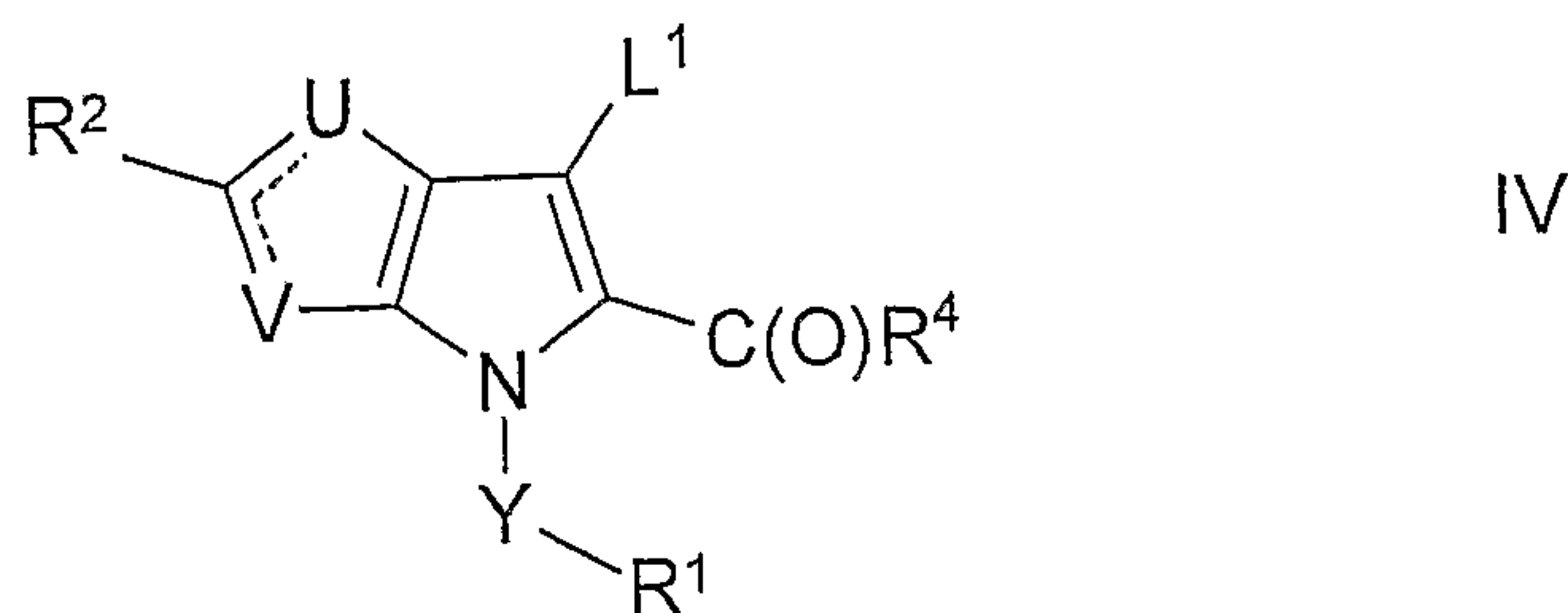


wherein the dotted lines, U, V, X¹, R² and R⁴ are as defined in Claim 1, with a compound of formula III,



wherein L¹ represents a suitable leaving group and R¹ and Y are as defined in Claim 1;

(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 the dotted lines, U, V, R¹, R², R⁴ and Y are as defined in Claim 1 and L¹ is as defined above, with a compound of formula V,



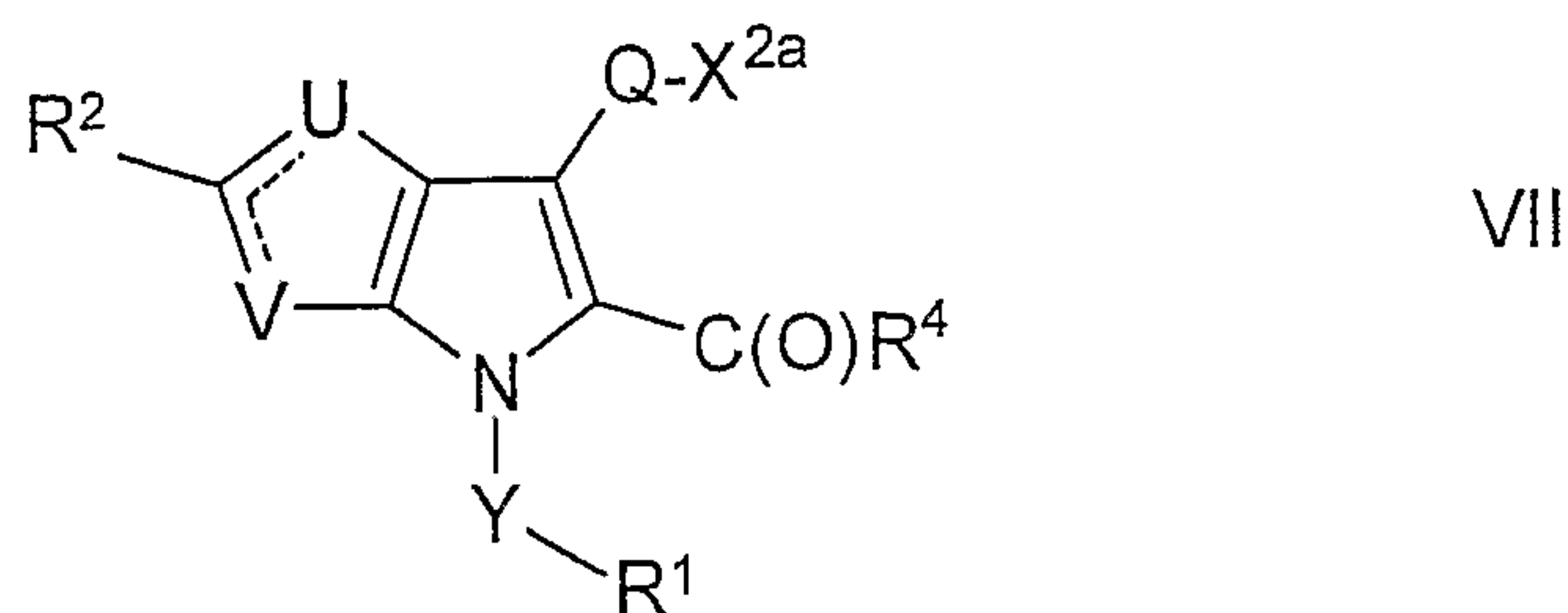
wherein Q^a represents a single bond or -C(O)-, L² represents a suitable leaving group and X² is as defined in Claim 1;

- (iii) for compounds of formula I in which X¹ represents -Q-X² and Q represents -C(O)-, reaction of a compound of formula I in which X¹ represents H with a compound of formula V in which Q^a represents -C(O)-;
- (iv) for compounds of formula I in which X¹ represents -N(R⁸)-J-R⁹ or -Q-X² 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(R⁸)-J-R⁹ or -Q-X² in which Q represents -O- or -S- and R⁸, J, R⁹ and X² are as defined in Claim 1;

- (v) for compounds of formula I in which X¹ represents -Q-X² and Q represents -S-, reaction of a compound of formula I in which X¹ represents H, with a compound of formula VI in which X^{1b} represents -Q-X², Q represents -S- and X² is as defined in Claim 1;
- (vi) for compounds of formula I in which X¹ represents -Q-X² 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 X¹ represents -Q-X², X² represents C₁₋₈ alkyl substituted by G¹, G¹ represents -A¹-R^{14a}, A¹ represents -N(R^{15a})A⁴- and A⁴ is a single bond (provided that Q represents a single bond when X² represents substituted C₁ alkyl), reaction of a compound of formula VII,



wherein X^{2a} represents a C₁₋₈ alkyl group substituted by a Z¹ group in which Z¹ represents =O, Q is as defined in Claim 1, provided that it represents a single bond

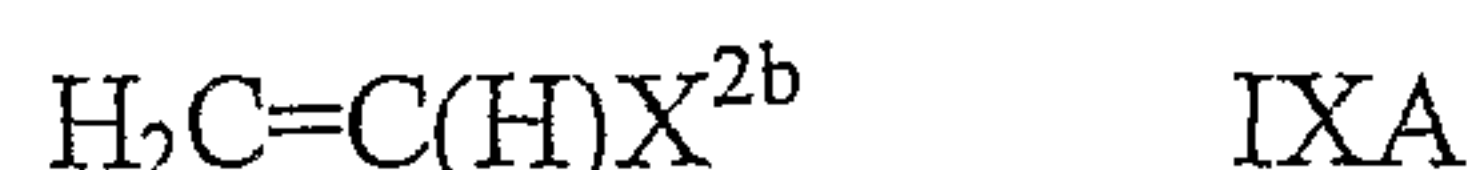
when X^{2a} represents C_1 alkyl substituted by $=O$, and the dotted lines, U , V , R^1 , R^2 , R^4 and Y are as defined in Claim 1 under reductive amination conditions in the presence of a compound of formula VIII,



5 wherein R^{14a} and R^{15a} are as defined in Claim 1;

(vii) 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 $-A^1-R^{14a}$, A^1 represents $-N(R^{15a})A^4-$ 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
10 (or equivalent reagent) 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
15 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,



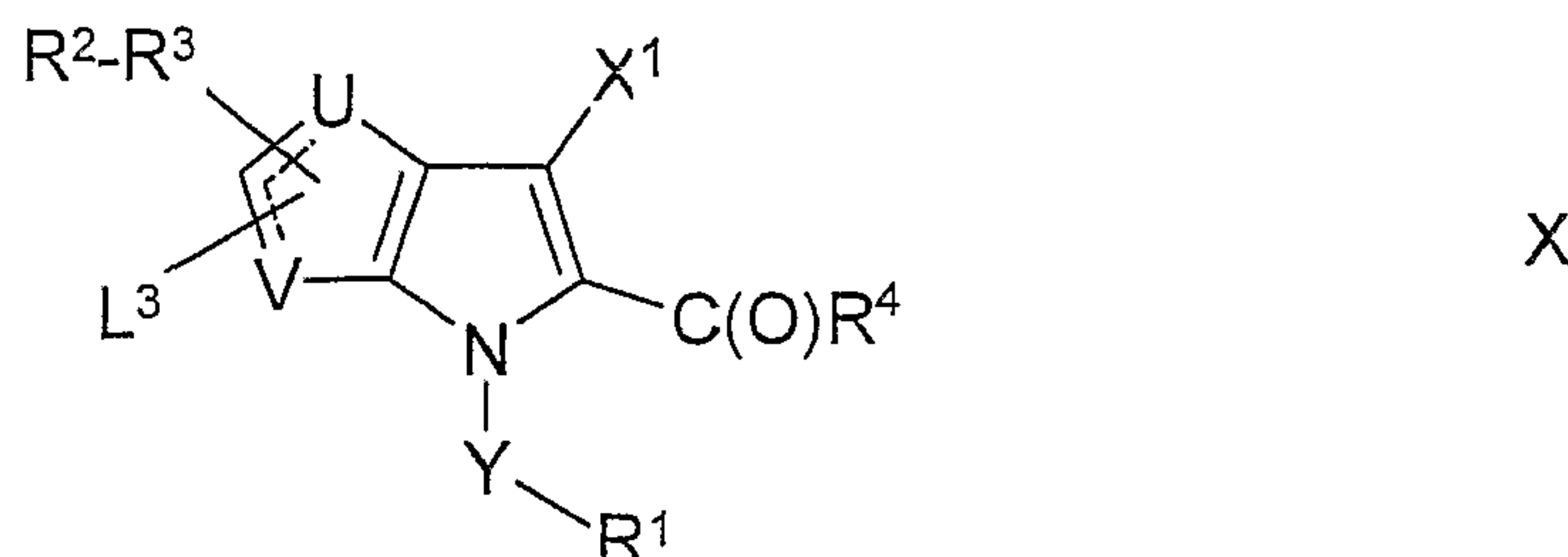
20 or the like, or a compound of formula IXC,



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;

25 (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, C_{2-8} alkenyl, cycloalkenyl or heterocycloalkenyl, reduction of a corresponding compound of formula I in which X^2 represents optionally substituted C_{2-8} alkenyl, cycloalkenyl, heterocycloalkenyl, C_{2-8} alkynyl,
30 cycloalkynyl or heterocycloalkynyl (as appropriate);

(x) for compounds of formula I in which D represents a single bond, -C(O)-, -C(R⁶)(R⁷)-, C₂₋₄ alkylene or -S(O)₂-, reaction of a compound of formula X,



5 wherein L³ represents L¹ or L² as defined above, which group is attached to one or both of the two carbon atoms of the thienoid ring of the thienopyrrole, R²-R³ represents whichever other substituent on the thienoid ring is already present in that ring, and the dotted lines, U, V, X¹, R¹, R², R³, R⁴ and Y are as defined in Claim 1, with a compound of formula XI,



wherein D^a represents a single bond, -C(O)-, -C(R⁶)(R⁷)-, C₂₋₄ alkylene or -S(O)₂-, L⁴ represents L¹ (when L³ is L²) or L² (when L³ is L¹), E, R⁶ and R⁷ are as defined in Claim 1 and L¹ and L² are as defined above;

(xi) for compounds of formula I in which 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,

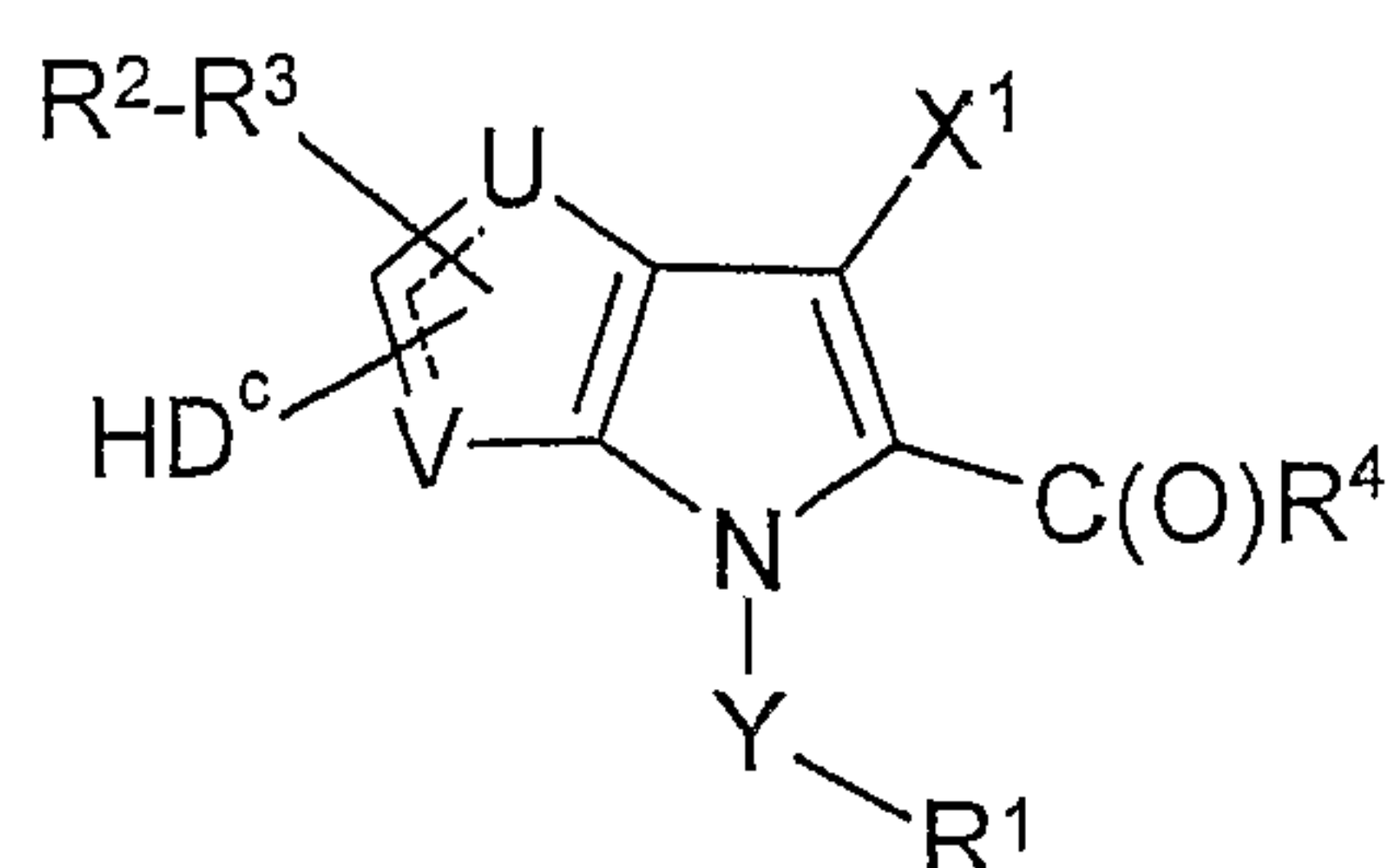


20 wherein D^b represents -S-, -O- or C₂₋₄ alkynylene in which the triple bond is adjacent to E and E is as defined in Claim 1;

(xii) for compounds of formula I in which 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 D represents -O- or -S-, reaction of a compound of formula XIII,

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XIII

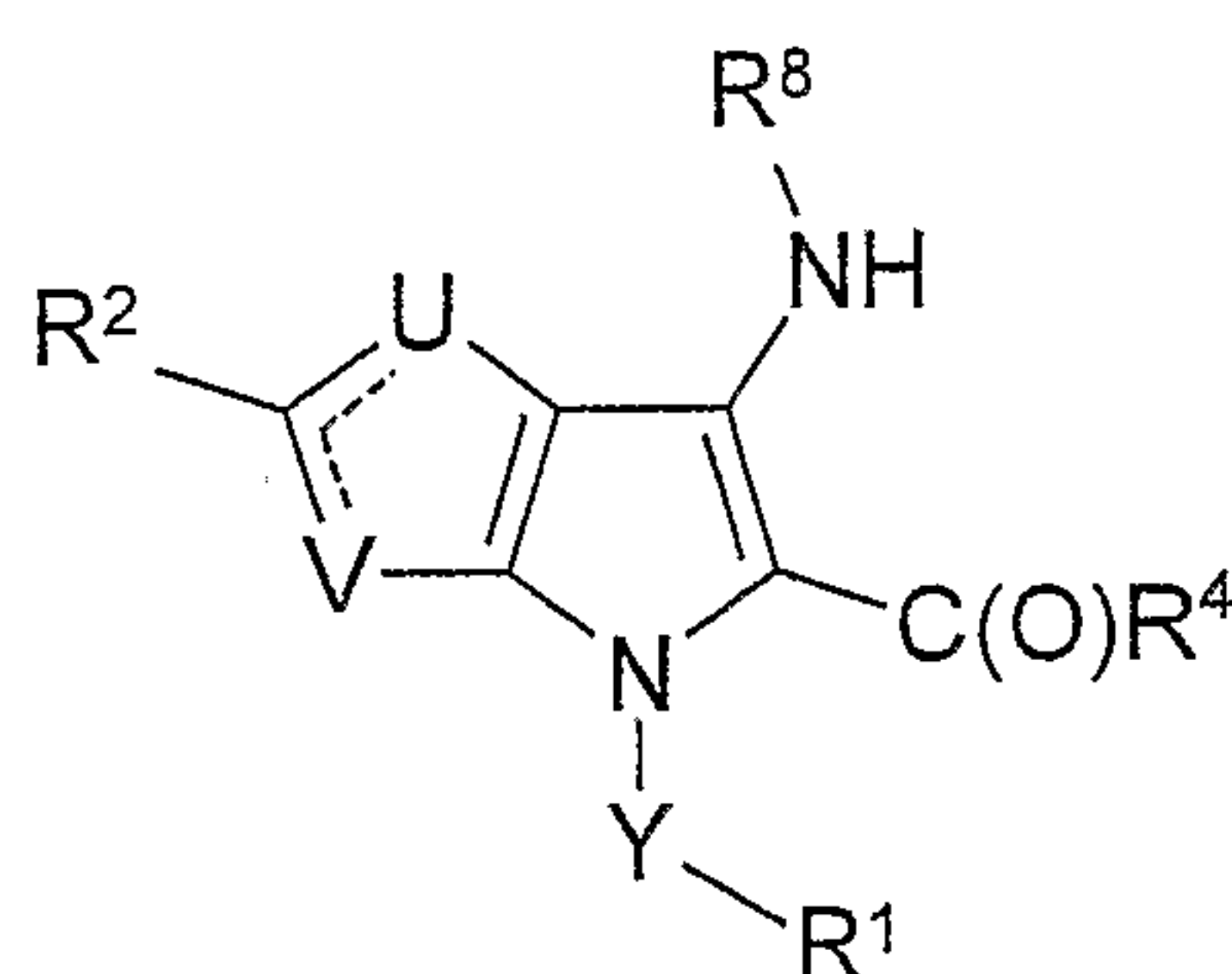
wherein the $-D^c-H$ group is attached to one or both of the two carbon atoms of the thienoid ring of the thienopyrrole, D^c represents $-O-$ or $-S-$ and the dotted lines, U, V, X^1 , R^1 , R^4 and Y are as defined in Claim 1 and R^2-R^3 is as defined above, with

5 a compound of formula XIV,



wherein L^2 is as defined above and E is as defined in Claim 1;

(xiv) for compounds of formula I in which X^1 represents $-N(R^8)-J-R^9$, reaction of a compound of formula XV,



XV

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wherein the dotted lines, U, V, R^1 , R^2 , R^4 , Y and R^8 are as defined in Claim 1, with a compound of formula XVI,

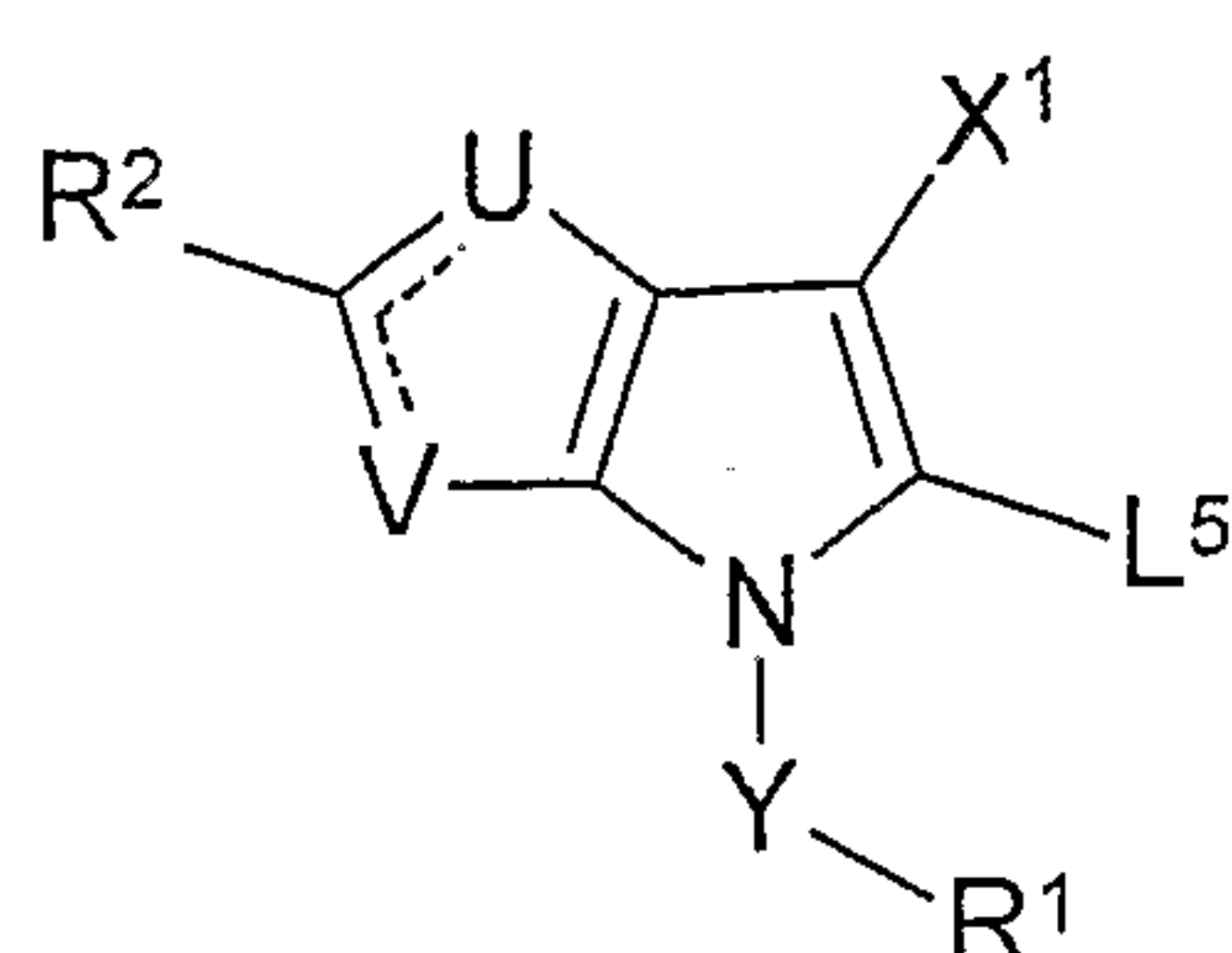


wherein J and R^9 are as defined in Claim 1 and L^1 is as defined above;

15 (xv) for compounds of formula I in which X^1 represents $-N(R^8)-J-R^9$, J represents a single bond and R^9 represents a C_{1-8} alkyl group, reduction of a corresponding compound of formula I, in which J represents $-C(O)-$ and R^9 represents H or a C_{1-7} alkyl group;

(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 reagents known to be a source of halo atoms;

20 (xvii) for compounds of formula I in which R^4 represents $-OR^{12a}$ in which R^{12a} is other than H, reaction of a compound of formula XVII,



XVII

wherein L^5 represents an appropriate alkali metal group, a -Mg-halide, a zinc-based group or a suitable leaving group, or a protected derivative thereof, and the dotted lines, U, V, X^1 , R^1 , R^2 and Y are as defined in Claim 1, with a compound of
 5 formula XVIII,



wherein R^{12za} represents R^{12a} provided that it does not represent H, and L^6 represents a suitable leaving group;

(xviii) for compounds of formula I in which R^4 represents $-OR^{12a}$ and R^{12a} is H,
 10 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;

(xix) for compounds of formula I in which R^4 represents $-OR^{12a}$, reaction of a
 15 corresponding 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^{12a} is as defined in Claim 1, and an appropriate catalyst system;

20 (xx) for compounds of formula I in which R^4 represents $-OR^{12a}$ in which R^{12a} represents H, hydrolysis of a corresponding compound of formula I in which R^{12a} does not represent H;

(xxi) for compounds of formula I in which R^4 represents $-OR^{12a}$ and R^{12a} does not represent H:

25 (A) esterification of a corresponding compound of formula I in which R^{12a} represents H; or

(B) trans-esterification of a corresponding compound of formula I in which R^{12a} does not represent H (and does not represent the same value of R^{12a} as the compound of formula I to be prepared),

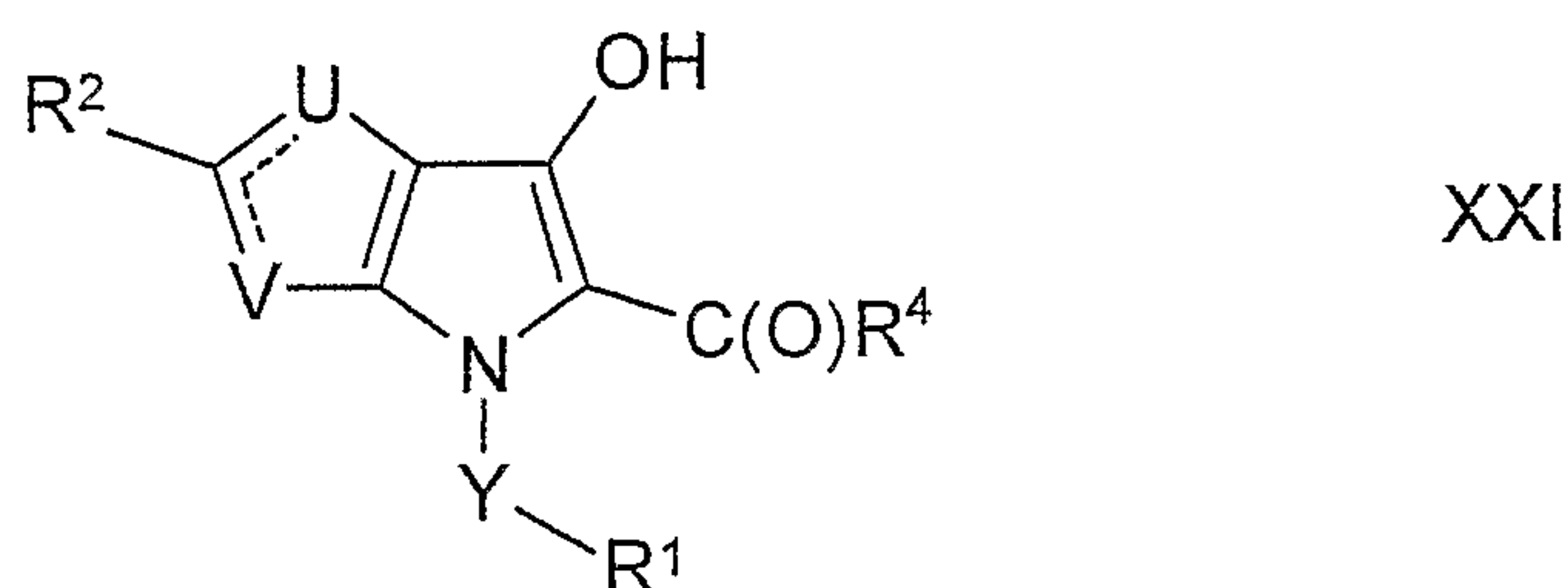
in the presence of the appropriate alcohol of formula XIX as defined above but in which R^{12a} represents R^{12za} as defined above;

(xxii) for compounds of formula I in which R^4 represents $-N(R^{12b})R^{13b}$, reaction of a corresponding compound of formula I in which R^4 represents $-OR^{12a}$ with a compound of formula XX,



wherein R^{12b} and R^{13b} are as defined in Claim 1;

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



wherein the dotted lines, U, V, R^1 , R^2 , R^4 and Y are as defined in Claim 1, with a compound of formula XXII,



wherein L^7 represents a suitable leaving group and X^2 is as defined in Claim 1;

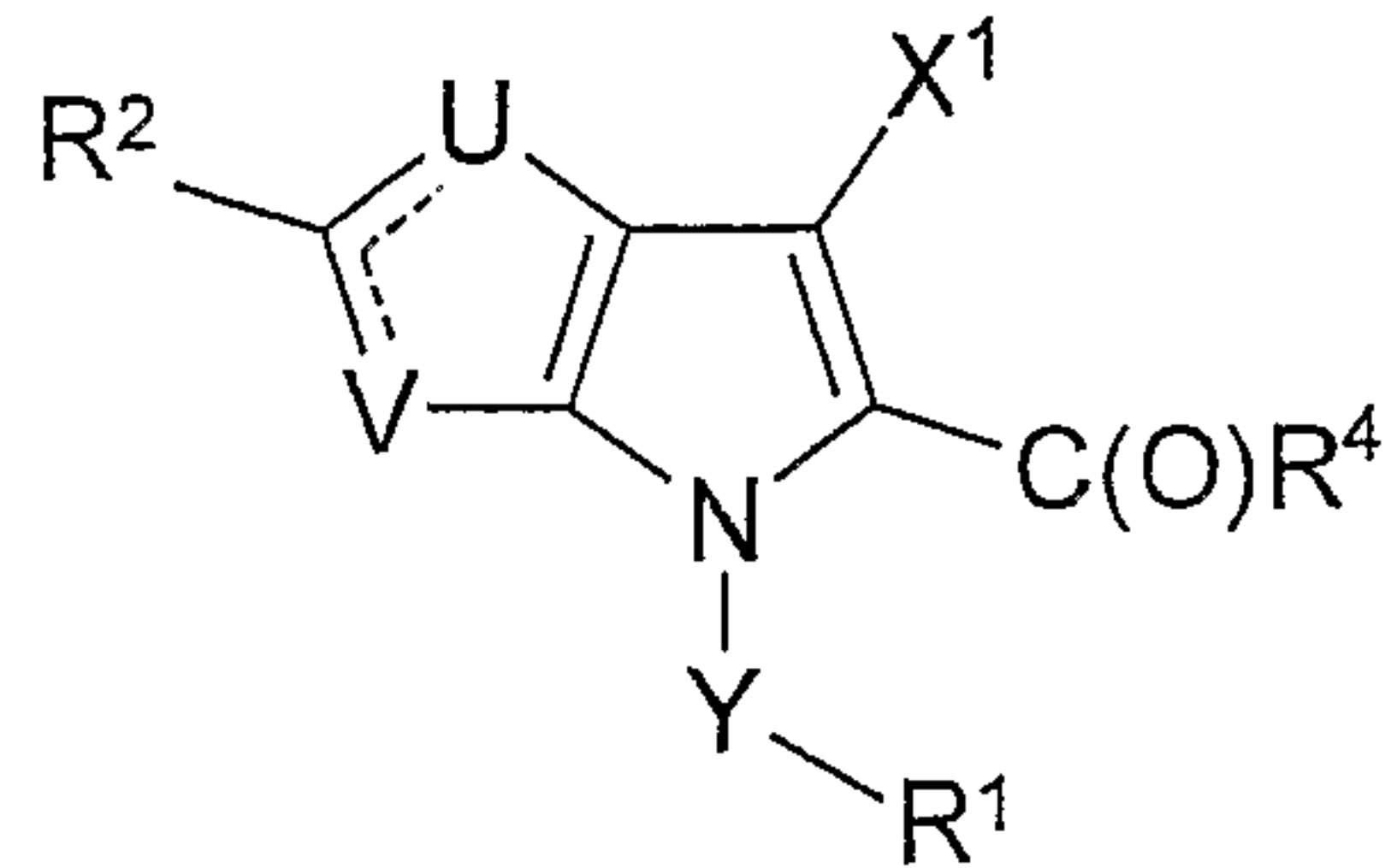
(xxiv) for compounds of formula I in which X^1 represents $-N(R^8)-J-R^9$, reaction of a compound of formula XXI as defined above, with a compound of formula VI in which X^{1b} represents $-N(R^8)-J-R^9$ and R^8 , R^9 and J are as defined in Claim 1;

(xxv) 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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 $=O$;

(xxvi) 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} 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;

(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, 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 $-A^1-R^{14a}$, A^1 represents $-OA^5-$, A^5 represents a single bond and R^{14a} represents H; or

(xxviii) 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 $=O$.



(I)