INDOLE DERIVATIVES USEFUL AS ENDOTHELIN RECEPTOR ANTAGONISTS

This invention relates to indole derivatives useful in the treatment of a variety of diseases including restenosis, renal failure and pulmonary hypertension, and to pharmaceutical formulations containing such compounds.

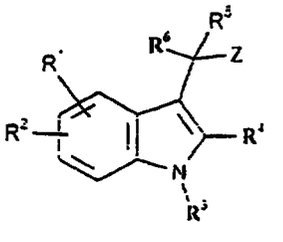
International Patent Application WO 94/14434 discloses indole derivatives which are indicated as endothelin receptor antagonists. European Patent Application 617001 discloses a large number of phenoxyphenylacetic acid derivatives which are also indicated as endothelin receptor antagonists.

Bergman *et al*, Tetrahedron, Vol 31, N° 17, 1975, pages 2063-2073, disclose a number of indole-3-acetic acids. Similar compounds are disclosed by Rusinova *et al*, Khim Geterotsikl Soedin, 1974, (2), 211-213 (see also Chemical Abstracts, Vol 81, N° 7, 19 August 1974, abstract N° 37455a), and Yarovenko *et al*, J Gen Chem USSR (English translation), Vol 39, 1969, page 2039 (see also Beilstein, Registry Number 431619). These compounds are not indicated in any kind of therapy, and proviso (i) below relates to them.

Julian *et al*, J Chem Soc, Chemical Communications, N° 1, 1973, disclose an N-p-chlorobenzoylindole derivative as a by-product of a photo-addition reaction. The compound is not indicated in any kind of therapy, and proviso (ii) below relates to it.

Yamamoto *et al*, Japanese Patent N° 70 041 381 (see also Chemical Abstracts, Vol 75, N° 3, 1971, abstract N° 20189v), disclose an N-p-chlorobenzoylindole derivative which is indicated as an anti-inflammatory. Proviso (iii) below relates to it.

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



I

wherein

R^1 and R^2 are optional substituents and independently represent C_{1-6} alkyl. C_{2-6} alkenyl [optionally substituted by CO_2H or $CO_2(C_{1-6}$ alkyl)]. C_{2-6} alkynyl. halogen. C_{1-3} perfluoroalkyl. $(CH_2)_mAr^1$. $(CH_2)_mHet^1$. $(CH_2)_mCONR^7R^8$. $(CH_2)_mCO_2R^8$. $O(CH_2)_qCO_2R^8$. $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$. $O(CH_2)_pOR^8$. $(CH_2)_mNR^7R^8$, $CO_2(CH_2)_qNR^7R^8$. $(CH_2)_mCN$. $S(O)_nR^8$, $SO_2NR^7R^8$. $CONH(CH_2)_mAr^1$ or $CONH(CH_2)_mHet^1$;

R^3 represents H, C_{1-6} alkyl. $(CH_2)_pNR^9R^{10}$. SO_2R^{10}. $SO_2NR^9R^{10}$. $(CH_2)_mCOR^{10}$. C_{2-6} alkenyl, C_{2-6} alkynyl. $(CH_2)_mCONR^9R^{10}$, $(CH_2)_mCO_2R^{10}$. $(CH_2)_pCN$. $(CH_2)_pR^{10}$ or $(CH_2)_pOR^{10}$;

R^4 and R^9 independently represent H or C_{1-6} alkyl;

R^7 represents H, C_{1-6} alkyl or C_{1-6} alkoxy;

R^5 represents H or OH;

R^6 represents phenyl optionally fused to a saturated or unsaturated 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, S and O, the group as a whole being optionally substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen, and wherein any members of the heterocyclic ring which are S may be substituted by one or two oxygen atoms;

R^8 and R^{10} independently represent H, C_{1-6} alkyl, Ar^2, Het^2 or C_{1-6} alkyl substituted by Ar^2 or Het^2;

Z represents CO_2H. CONH(tetrazol-5-yl). $CONHSO_2O(C_{1-4}$ alkyl). CO_2Ar^3, $CO_2(C_{1-6}$ alkyl), tetrazol-5-yl, $CONHSO_2Ar^3$, $CONHSO_2(CH_2)_qAr^3$ or $CONHSO_2(C_{1-6}$ alkyl);

m represents 0, 1, 2 or 3;

n represents 0, 1 or 2;

p represents 2, 3 or 4;

q represents 1, 2 or 3;

Ar^{1-3} independently represent phenyl, naphthyl, or an aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which aromatic heterocycle is optionally fused to a benzene ring, and which phenyl group is optionally fused to an aromatic heterocycle as defined immediately above, the group as a whole being optionally substituted by one or more groups falling within the definition of R^1 above; and

Het^1 and Het^2 independently represent a non-aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which group is optionally

substituted by one or more groups falling within the definition of R^1 above, and is further optionally substituted by =O or =S;

provided that:

(i) when R^1 represents methoxy or is absent, R^2 is absent, R^3 represents H, R^4 represents H, methyl or ethyl, and R^6 represents unsubstituted phenyl, then Z does not represent CO_2H or $CO_2(C_{1-6}$ alkyl);

(ii) when R^1 and R^2 are absent, R^3 represents $CO(p\text{-}ClC_6H_4)$, R^4 represents H, and R^6 represents unsubstituted phenyl, then Z does not represent $CO_2(C_{1-6}$ alkyl); and

(iii) when R^1 represents methoxy, R^2 is absent, R^3 represents $CO(p\text{-}ClC_6H_4)$, R^4 represents methyl, and R^6 represents unsubstituted phenyl, then Z does not represent CO_2H;

or a pharmaceutically acceptable derivative thereof.

Pharmaceutically acceptable derivatives include those compounds in which the functional groups explicitly recited above have been derivatised to provide prodrugs which can be converted to the parent compound *in vivo*. Such prodrugs are discussed in Drugs of Today, Vol 19, 499-538 (1983) and Annual Reports in Medicinal Chemistry, Vol 10, Ch 31 p306-326. In addition, pharmaceutically acceptable derivatives include pharmaceutically acceptable salts, such as alkali metal salts (for example sodium salts) of any acidic groups that may be present.

"Halogen" includes fluorine, chlorine, bromine and iodine.

Alkyl groups which R^{1-4}, R^{6-10} and Z represent or comprise may be straight chain, branched or cyclic.

Besides phenyl and naphthyl, specific groups that Ar^{1-3} may represent or comprise include indolyl, pyridinyl, thienyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl, imidazolyl, thiazolinidyl, isoxazolyl, oxadiazolyl, thiadiazolyl, pyrrolyl and pyrimidinyl.

Specific groups that Het^1 and Het^2 may represent or comprise include oxazolidinyl, triazolethione, triazolone, oxadiazolone, oxadiazolethione, imidazolidinyl, morpholinyl, piperidinyl and piperazinyl.

Preferred groups of compounds which may be mentioned include those in which:

(a) R^1 represents halogen, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$ or $(CH_2)_mCN$. In these groups it is preferred that R^7 and R^8 represent H or C_{1-6} alkyl. Preferably, m is 0 or 1. Thus, specific groups which may be mentioned are $CONH_2$, CO_2H, CH_2OH, F or CH_3CO. R^1 is preferably attached to the 6-position of the indole ring.

(b) R^2 is absent (i.e. its place on the indole ring is occupied by H).

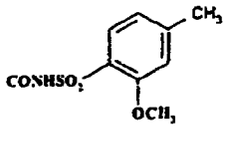
(c) R^3 represents H, C_{1-6} alkyl or $(CH_2)_pOR^{10}$. Preferably, R^{10} is C_{1-6} alkyl and p is 2. Thus, specific groups which may be mentioned are methyl and $(CH_2)_2OCH_3$.

(d) R^4 represents H.

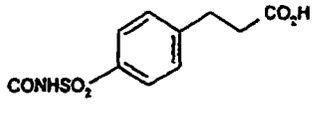
(e) R^5 represents H.

(f) R^6 represents phenyl fused to a saturated 5-membered heterocyclic ring, for example 3,4-methylenedioxyphenyl.

(g) Z represents CO_2H or $CONHSO_2Ar^3$. Preferably, Ar^3 is phenyl substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy and C_{1-6} alkyl substituted by carboxy. Thus, specific groups which may be mentioned are:

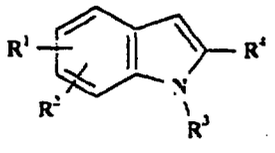


and



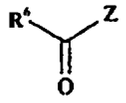
There is further provided a process for the production of the compounds of the invention, comprising:

(a) when R^5 represents H, reaction of a compound of formula IIA,



IIA

wherein R^{1-4} are as defined above, with a compound of formula III.

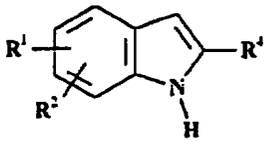


III

wherein R^b and Z are as defined above. in the presence of a Lewis acid or trifluoroacetic acid, and a tri(C_{1-6} alkyl)silane:

(b) when R^5 represents OH. reaction of a compound of formula IIA. as defined above. with a compound of formula III. as defined above, in the presence of a Lewis acid;

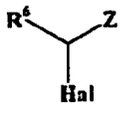
(c) when R^3 represents H and R^5 represents H. treatment of a compound of formula IIB,



IIB

wherein R^1. R^2 and R^4 are as defined above. with a Grignard reagent. followed by reaction with a compound of formula III. as defined above, followed by treatment with a Lewis acid or trifluoroacetic acid. and a tri(C_{1-6} alkyl)silane:

(d) when R^3 represents H and R^5 represents H. treatment of a compound of formula IIB, as defined above, with a Grignard reagent. followed by reaction with a compound of formula IV,



IV

wherein R^6 and Z are as defined above. and Hal represents halogen:

(e) when R^5 represents H, reaction of a compound of formula IIA. as defined above. with a compound of formula IV. as defined above. in the presence of a hindered, non-nucleophilic base;

(f) reacting a compound of formula I. in which R^1 represents Br. with CO gas in the presence of a palladium catalyst and a reducing agent. to provide the corresponding compound of formula I in which R^1 represents CHO;

(g) reacting a compound of formula I. in which R^1 represents Br. with CO gas in the presence of a palladium catalyst and a C_{1-6} alkanol. to provide the corresponding compound of formula I in which R^1 represents $CO_2(C_{1-6}$ alkyl):

(h) coupling a compound of formula I in which Z represents CO_2H with a compound of formula VI.

$H_2NSO_2Ar^3$ VI

wherein Ar^3 is as defined above. to provide the corresponding compound of formula I in which Z represents $CONHSO_2Ar^3$; or

(i) reacting a compound of formula I. in which R^1 represents Br, with an alkyl lithium reagent and quenching with dimethylformamide or carbon dioxide. to give a corresponding compound in which R^1 represents CHO or CO_2H respectively;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable derivative thereof or vice versa.

In process (a), suitable Lewis acids include boron trifluoride diethyletherate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dichloromethane. at a temperature below room temperature. for example -40 to -78°C. A preferred tri(C_{1-6} alkyl)silane is triethylsilane. Intermediate compounds in which R^5 represents OH may be isolated from this process.

In process (b), suitable Lewis acids include boron trifluoride diethyletherate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dichloromethane. at a temperature below room temperature, for example -40 to -78°C. The reaction is followed by basic work up.

In process (c), suitable Grignard reagents include methylmagnesium iodide. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example toluene, below room temperature, for example -70°C. Suitable Lewis acids include boron trifluoride diethyletherate. The acid treatment may be carried out in a solvent which does not adversely affect the reaction. for example dichloromethane, at a temperature of 0°C to room temperature. A preferred tri(C_{1-6} alkyl)silane is triethylsilane.

In process (d), suitable Grignard reagents include methylmagnesium iodide. The reaction is preferably carried out in a solvent which does not adversely affect the reaction. for example toluene. at or around room temperature. The reaction mixture may be worked up with a weak acid such as aqueous ammonium chloride. Hal is preferably Br.

In process (e), suitable hindered non-nucleophilic bases include 2,6-dimethylpyridine. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example 80°C.

In process (f), suitable palladium catalysts include dichlorobis(triphenylphosphine)-palladium(II). Suitable reducing agents include sodium formate. The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example 110°C.

In process (g), suitable palladium catalysts include dichlorobis(triphenylphosphine)-palladium(II). The reaction is preferably carried out in a solvent which does not adversely affect the reaction, for example dimethylformamide, at an elevated temperature, for example the reflux temperature of the reaction mixture.

In process (h), the reaction may be facilitated by the use of conventional coupling agents, for example N,N-carbonyl diimidazole. When using this agent, the acid is first reacted with the agent (for example in dichloromethane at the reflux temperature of the solvent), and then the product of this reaction is reacted with the amine (preferably in the presence of a strong hindered amine base such as 1,8-diazabicyclo[5.4.0]undec-7-ene, in a solvent such as dichloromethane at the reflux temperature of the solvent). An alternative agent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide which reacts at room temperature.

In process (i), suitable alkyl lithium reagents include n-butyl lithium. The reaction is carried out by adding the alkyl lithium reagent to the compound of formula I in a solvent such as tetrahydrofuran, at a temperature below room temperature (for example -40 to -78°C), and stirring for about 2 hours. Dimethylformamide or solid carbon dioxide is then added and the reaction mixture allowed to warm to room temperature.

Compounds of formulae IIA, IIB, III, IV and VI are either known or may be prepared by conventional methods well known to those skilled in the art. For example, compounds of formulae IIA and IIB may be prepared by the Fischer, Reissert and Madelung syntheses. In addition, International Patent Application WO 94/14434 discloses a number of routes to

2-carboxy indole derivatives (see page 8 onwards) which may be decarboxylated readily (using copper and quinoline) to give compounds of formulae IIA or IIB in which R^4 is H, or reduced to give compounds of formulae IIA or IIB in which R^4 is alkyl. Other methods for the preparation of indoles are described by Moyer et al. J Org Chem. 1986. 51. 5106-5110; Wender et al. Tetrahedron. 1983. 39 N° 22, 3767-3776; Uhle. J Am Chem Soc. 1949, 71. 761: Uhle et al. J Am Chem Soc, 1960, 82. 1200; Nagasaka et al, Heterocycles, 1977, 8. 371; Bowman et al, J Chem Soc. Perkin Trans 1, 1972. 1121: Bowman et al. J Chem Soc, Perkin Trans 1, 1972. 1926; and Clark et al, Heterocycles, 1984, 22, 195.

Compounds of formula III in which R^6 is an electron-rich group (for example 1,3-benzodioxole) and Z is $CO_2CH_2CH_3$ may be prepared by a Friedel-Crafts acylation between a compound of formula R^6H and the compound of formula $ClCOCO_2CH_2CH_3$. The reaction is preferably carried out in the presence of a Lewis acid (for example $AlCl_3$), in a solvent which does not adversely affect the reaction, for example dichloromethane, below room temperature (for example 0°C).

Compounds of formula III in which R^6 is not an electron-rich group (for example groups substituted by halogen or OH) and Z is CO_2CH_3 may be prepared by reaction of a compound of formula R^6Li with a compound of formula $CH_3OCOCO_2CH_3$. The reaction may be carried out in a solvent which does not adversely affect the reaction, for example tetrahydrofuran, below room temperature (for example -40°C to -78°C).

Compounds of formula R^6Li may be prepared by reacting a compound of formula R^6Br and butyl lithium. The reaction may be carried out in a solvent which does not adversely affect the reaction, for example tetrahydrofuran, below room temperature (for example -78°C).

Compounds of formula IV may be prepared by halogenating the corresponding alcohol with an agent such as hydrobromic acid. When Z represents $CO_2(C_{1-6}$ alkyl), compounds of formula $R^6CH(OH)Z$ may be prepared by reacting an aldehyde of formula R^6CHO with bromoform under basic conditions, and treating the crude carboxylic acid intermediate with a C_{1-6} alkanol.

Compounds of formula I may be converted into other compounds of formula I using known techniques. Processes (f)-(i) above are such conversions of particular interest.

Compounds of formulae I, III or IV in which Z represents a carboxylic ester may be converted into corresponding compounds in which Z represents other groups by conventional methods.

Compounds of formulae I, IIA or IIB in which R^3 represents H may be converted to corresponding compounds in which R^3 is other than H by conventional methods. In general, R^3 groups other than H may be added by treatment of a compound of formula I, IIA or IIB in which R^3 represents H with sodium hydride, followed by an appropriate compound of formula R^3Br or R^3I, in dimethylformamide at 0°C. Preferably, compounds of formulae I, IIA or IIB in which R^3 represents electron-withdrawing groups (such as SO_2R^{10}, $SO_2NR^9R^{10}$, $CONR^9R^{10}$ and COR^{10}) are prepared by reacting a compound of formula I, IIA or IIB in which R^3 represents H with an appropriate compound of formula R^3Cl.

The compounds of the invention may be separated and purified by conventional methods.

It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional techniques, for example as described in 'Protective Groups in Organic Synthesis' by T W Greene and P G M Wuts, John Wiley and Sons Inc, 1991. For example, it may be desirable to protect the indole nitrogen of a compound of formula IIA and use the method of process (a) followed by deprotection to give a compound of formula I in which R^3 represents H. Processes (a)-(h) embrace such protection and deprotection steps.

The synthesis of triazolethione, oxadiazolone and oxadiazolethione is described in J Med Chem. 1993, 36, 1090-1099. The synthesis of oxathiadiazole is described in Bioorganic and Medicinal Chemistry Letters, 1994, 4 N° 1, 41-44.

The compounds of the invention may possess one or more chiral centres and so exist in a number of stereoisomeric forms. All stereoisomers and mixtures thereof are included in the scope of the present invention. Racemic compounds may either be separated using preparative HPLC and a column with a chiral stationary phase or resolved to yield individual enantiomers utilising methods known to those skilled in the art. In addition, chiral intermediate compounds may be resolved and used to prepare chiral compounds of formula I.

The compounds of the invention are useful because they have pharmacological activity in animals, including humans. More particularly, they are useful in the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia and cyclosporin induced nephrotoxicity. The treatment of restenosis, renal failure and pulmonary hypertension are of particular interest. The compounds of the invention may be administered alone or as part of a combination therapy.

Thus, according to a further aspect of the invention, there is provided a compound of formula I, as defined above, but without provisos (i) and (ii), or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.

There is further provided a pharmaceutical formulation comprising a compound of formula I, as defined above, but without provisos (i) and (ii), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention also provides the use of a compound of formula I, as defined above, but without provisos (i)-(iii), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity. The invention also provides a method of treatment of these diseases, which comprises administering a therapeutically effective amount of a compound of formula I, as defined

above. but without provisos (i)-(iii). or a pharmaceutically acceptable derivative thereof. to a patient in need of such treatment.

Without being limited by theory. the compounds of the invention are believed to be endothelin receptor antagonists. Endothelin (ET) is a potent vasoconstrictor synthesised and released by endothelial cells. There are three distinct isoforms of ET: ET-1, ET-2 and ET-3. all being 21-amino acid peptides and herein the term 'endothelin' refers to any or all of the isoforms. Two receptor subtypes, ET_A and ET_B have been pharmacologically defined (see for example H. Arai et al, *Nature*, **348**. 730 , 1990) and further subtypes have recently been reported. Stimulation of ET_A promotes vasoconstriction and stimulation of ET_B receptors causes either vasodilation or vasoconstriction.

The effects of endothelin are often long-lasting and. as the endothelins are widely distributed in mammalian tissues. a wide range of biological responses have been observed in both vascular and non-vascular tissue. The main effects of endothelin are observed in the cardiovascular system, particularly in the coronary. renal, cerebral and mesenteric circulation.

Increased circulating levels of endothelin have been observed in patients who have undergone percutaneous transluminal coronary angioplasty (PTCA) (A.Tahara et al. *Metab. Clin. Exp.* **40**. 1235. 1991) and ET-1 has been found to induce neointimal formation in rats after balloon angioplasty (S.Douglas et al. *J.Cardiovasc.Pharm.*, **22** (Suppl 8). 371. 1993). The same workers have found that an endothelin antagonist. SB-209670. causes a 50% reduction in neointimal formation relative to control animals (S.Douglas et al. *Circ Res*, 75, 1994). Antagonists of the endothelin receptor may thus be useful in preventing restenosis post PTCA.

Endothelin-1 is produced in the human prostate gland and endothelin receptors have been identified in this tissue. Since endothelin is a contractile and proliferative agent endothelin antagonists could be useful in the treatment of benign prostate hypertrophy.

There is widespread localisation of endothelin and its receptors in the central nervous system and cerebrovascular system (R.K.Nikolov et al. *Drugs of Today*. 28(5). 303. 1992) with ET being implicated in cerebral vasospasm. cerebral infarcts and neuronal death. Elevated levels of endothelin have also been observed in patients with:

- Chronic renal failure (F.Stockenhuber et al. *Clin Sci* (Lond.). 82. 255. 1992)
- Ischaemic Heart Disease (M.Yasuda. *Am. Heart J.*. 119. 801. 1990)
- Stable or unstable angina (J.T.Stewart. *Br. Heart J.* 66. 7 1991)
- Pulmonary Hypertension (D.J.Stewart et al. *Ann. Internal Medicine*. 114. 464. 1991)
- Congestive heart failure (R.J.Rodeheffer et al. *Am.J.Hypertension*. 4. 9A. 1991)
- Preeclampsia (B.A.Clark et al. *Am.J.Obstet.Gynecol.*. 166. 962. 1992)
- Diabetes (A.Collier et al. *Diabetes Care*, 15 (8). 1038. 1992)
- Crohn's disease (S.H.Murch et al. *Lancet*. 339. 381. 1992)
- Atherosclerosis (A.Lerman et al. *New Eng. J. Med.*. 325. 997. 1991)

In every case the disease state associated with the physiologically elevated levels of endothelin is potentially treatable with an endothelin receptor antagonist and hence a compound of the invention.

Compounds that selectively antagonise the ET_A receptor rather than the ET_B receptor are preferred.

The biological activity of the compounds of the invention may be demonstrated in Tests A-C below:

A. **Binding assay**

Competition between test compounds and ^{125}I-ET-1 binding to human endothelin receptors is determined as follows.

Binding to ET_A receptors

25ul of a 30pM solution of [^{125}I]Tyr^{13} ET-1 (specific activity 2.200Ci/mM) is mixed with 25µl samples of test compound (final concentrations in the range 0.1nM - 50.000nM).

200µl of a solution containing cloned human ET_A receptor (0.75pmoles receptor protein/ml), 50mM Tris, 0.5mM $CaCl_2$, 0.1% human serum albumen, 0.1% bacitracin, 0.05% Tween 20, pH 7.4 is added. The solution is mixed at 37°C for 2 hours. After the incubation, the unbound ligand is separated from receptor bound ligand by filtration with a Brandel cell harvester, followed by three washes of buffer. Filter papers are counted for radioactivity, and the IC_{50} (the concentration of test compound at which 50% of the radio-labelled compound is unbound) determined for the concentration range tested.

Binding to ET_B receptors

25µl of a 30pM solution of [^{125}I]Tyr^{13} ET-1 (specific activity 2.200Ci/mM) is mixed with 25µl samples of test compound (final concentration 0.1nM - 50.000nM). 200µl of a solution containing cloned human ET_B receptor (0.25pmoles receptor protein/ml), 50mM Tris, 0.5mM $CaCl_2$, 0.1% human serum albumen, 0.1% bacitracin, 0.05% Tween 20, pH 7.4 is added. The solution is mixed at 37°C for 2 hours. After the incubation, the unbound ligand is separated from receptor bound ligand by filtration with a Brandel cell harvester, followed by three washes of buffer. Filter papers are counted for radio-activity, and the IC_{50} (the concentration of test compound at which 50% of the radio-labelled compound is unbound) determined for the concentration range tested.

B. *In vitro* vascular smooth muscle activity

Rat aorta

Rat aortae are cleaned of connective tissue and fat and cut into helical strips approx 4mm in width. The endothelium is removed by dragging the luminal surface of the tissue gently across filter paper moistened with Krebs solution of composition (mM) NaCl 130, KCl 5.6, $NaHCO_3$ 25, Glucose 11.1, NaH_2PO_4 0.6, $CaCl_2$ 2.16, $MgCl_2$ 0.5, gassed with 95% O_2/5% CO_2. The strips are mounted in isolated organ baths in Krebs solution under a resting tension of 1gram. Organ bath solutions are maintained at 37°C and continuously aerated with 95% O_2/5% CO_2. Tensions are measured with Maywood Industries isometric force transducers and displayed on Gould TA4000 recorders. After equilibration in the organ bath for 1 hour, tissues are contracted by the addition of KCl to a final concentration of 60mM. The KCl is removed by replacing the Krebs solution with two further washes with

Krebs solution. To determine the potency of an ET_A receptor antagonist, two tissues are cumulatively dosed with ET-1 (0.1nM - 1μM); other tissues are dosed with ET-1 (0.1nM - 1μM) in duplicate, beginning 30 minutes after the inclusion in the organ bath medium of the test compound. Sufficient tissues are used per experiment to generate dose-response curves to ET-1 in the absence and the presence of at least 3 concentrations of antagonist. Data are expressed as the mean ± s.e.m. Dissociation constants (k_b) of competitive antagonists are calculated by the method of Arunlakshana and Schild.

Rabbit pulmonary artery

Isolated rabbit pulmonary arteries are cleaned of connective tissue and fat and cut into rings approx 4mm in width. The endothelium is removed by inserting a fibrous instrument moistened with Krebs solution of composition (mM) NaCl 130, KCl 5.6, $NaHCO_3$ 25, Glucose 11.1, NaH_2PO_4 0.6, $CaCl_2$ 2.16, $MgCl_2$ 0.5, gassed with 95% O_2/5% CO_2. The rings are mounted in isolated organ baths in Krebs solution under a resting tension of 1gram. Organ bath solutions are maintained at 37°C and continuously aerated with 95% O_2/5% CO_2. Tensions are measured with Maywood Industries isometric force transducers and displayed on Gould TA4000 recorders. After equilibration in the organ bath for 1 hour, tissues are contracted by the addition of KCl to a final concentration of 60mM. The KCl is removed by replacing the Krebs solution, with two further washes with Krebs solution. To determine the potency of an ET_B receptor antagonist, two tissues are cumulatively treated with BQ-3020 (0.1nM - 1μM); other tissues are treated with BQ-3020 (0.1nM - 1μM) in duplicate, beginning 30 minutes after the inclusion in the organ bath medium of the test compound. Sufficient tissues are used per experiment to generate dose-response curves to BQ-3020 in the absence and the presence of at least 3 concentrations of antagonist. Data are expressed as the mean = s.e.m. Dissociation constants (k_b) of competitive antagonists are calculated by the method of Arunlakshana and Schild.

C. *In vivo* blockade of endothelin-induced blood pressure elevation

In anaesthetised, ganglion-blocked and artificially respired rats, the left common carotid artery and the right jugular vein are cannulated for the measurement of arterial blood pressure and the administration of compound respectively. Rats are treated with the ET_B

antagonist BQ-788 (0.25mg/kg i.v.). Beginning 10 minutes after administering BQ-788. the hypertensive response to ET-1 (1μg/kg i.v.) is determined. When the blood pressure has returned to baseline. the test compound is administered (0.1 - 20mg/kg i.v.) and after 10 minutes the ET-1 challenge is repeated. Increasing concentrations of the test compound are administered. followed 10 minutes after each administration by a further ET-1 challenge. An IC_{50} is determined based upon inhibition of ET-1 induced pressor response upon cumulative dosing with compound.

Duration of blockade is determined in anaesthetised. ganglion-blocked and artificially respired rats. in which the left common carotid artery and the right jugular vein are cannulated for the measurement of arterial blood pressure and the administration of compound respectively. Rats are treated with the ET_B antagonist BQ-788 (0.25mg/kg i.v.). Beginning 10 minutes after administering BQ-788. the hypertensive response to ET-1 (1μg/kg i.v.) is determined. When the blood pressure has returned to baseline. the test compound is administered (10mg/kg i.v.). Further administrations of ET-1 are made 5, 20 and 60 minutes after dosing the test compound. In separate animals. prepared similarly, an ET-1 challenge is made 2 or 4 hours after dosing with the test compound. in these animals BQ-788 is dosed 10 minutes before the ET-1 challenge. For later time points. rats are dosed with the test compound (10mg/kg) i.v. *via* a tail vein or p.o., they are then anaesthetised and prepared for blood pressure measurement as above. In these rats, ET-1 (1μg/kg i.v.) was administered 6 or 8 hours after the test compound.

For human use the compounds of the invention can be administered alone but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example they can be administered orally in the form of tablets containing such excipients as starch or lactose or in capsules or ovules either alone or in admixture with excipients or in the form of elixirs. solutions or suspensions containing the compound or salt in a liquid carrier. for example a vegetable oil. glycerine or water with a flavouring or colouring agent. They can be injected parenterally. for example intravenously. intramuscularly or subcutaneously. For parental administration. they are best used as sterile aqueous solutions which may contain other substances. for example. enough glucose or salts to make the

solution isotonic with blood. For parenteral administration the compound or salt may also be administered as a solution or suspension in a suitable oil, for example polyethylene glycol, lecithin or sesame oil.

Compounds of the invention may also be administered through inhalation of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane.

For oral or parenteral administration to human patients the daily dosage levels of compounds of the invention will be from 0.01 to 30 mg/kg (in single or divided doses) and preferably will be in the range 0.01 to 5 mg/kg. Thus tablets will contain 1mg to 0.4g of compound for administration singly or two or more at a time, as appropriate. The above dosages are, of course only exemplary of the average case and there may be instances where higher or lower doses are merited, and such are within the scope of the invention.

Alternatively the compounds of the invention can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment or dusting powder or in the form of a medicated plaster, patch or membrane. For example they may be incorporated in a cream containing an aqueous emulsion of polyethylene glycols or liquid paraffin. The compounds may also be administered intranasally.

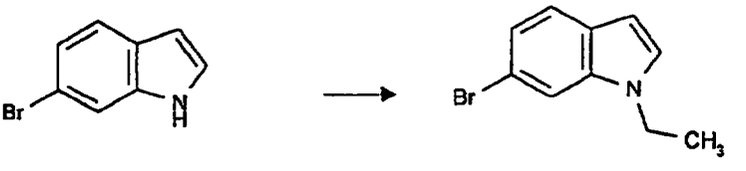
The invention is illustrated by the following Examples, in which the following abbreviations are used:

APCI	atmospheric pressure chemical ionisation
DMF	dimethylformamide
DMSO	dimethylsulphoxide
Et	ethyl
h	hour
iPr	isopropyl
LRMS	low resolution mass spectroscopy
min	minute
Me	methyl
NMR	nuclear magnetic resonance
TFA	trifluoroacetic acid
Tlc	thin layer chromatography

Example 1

Ethyl 2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl)acetate

(a) 6-Bromo-1-ethylindole

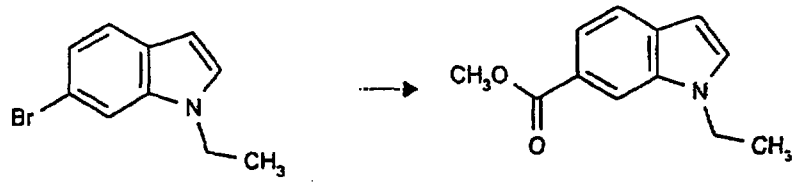


Sodium hydride (480mg of a 60% dispersion in mineral oil) was added to a stirred solution of 6-bromoindole (1.8g, 9.2mmol) in dimethylformamide (20ml) at 0°C under a nitrogen atmosphere. After 1 hour bromoethane (1.1ml, 14.7 mmol) was added and the cooling bath removed. After 12 hours the dimethylformamide was removed in vacuo. The residue was purified directly by flash column chromatography (using 95% hexane, 5% ethyl acetate as eluant) to give 2.1 g of the subtitle compound as a yellow oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.45 (t, 3H), 4.10 (q, 2H), 6.45 (d, 1H), 7.10 (d, 1H), 7.20 (d, 1H), 7.45 (d, 1H), 7.55 (s, 1H)

LRMS (Thermospray): 224 (MH^+)

(b) 6-Methoxycarbonyl-1-ethylindole

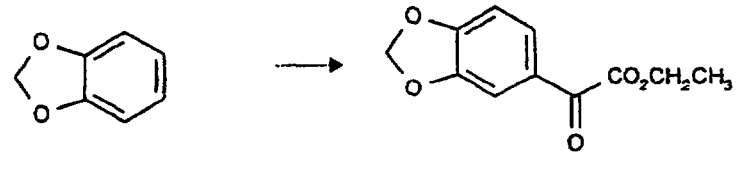


Sec-butyllithium (9.4ml of a 1.3M solution in cyclohexane) was added to a stirred solution of 6-bromo-1-ethylindole [the compound of step (a), 2.5g] in diethylether (20ml) at -78°C under a nitrogen atmosphere. After 30 minutes this solution was transferred by cannula to a stirred solution of methyl chloroformate (1.29ml, 16.74mmol) in diethyl ether (8ml) at -78°C under a nitrogen atmosphere. After 1 hour the cooling bath was removed and the mixture was allowed to warm to room temperature. After a further 1 hour the mixture was poured into brine and extracted with ethyl acetate. The organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Flash column chromatography (elution with 90% hexane, 10% ethyl acetate) gave 1.76g of the subtitle compound as a pale yellow oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.50 (t, 3H), 4.00 (s, 3H), 4.25 (q, 2H), 6.50 (d, 1H), 7.25 (d, 1H), 7.60 (d, 1H), 7.80 (d, 1H), 8.10 (s, 1H)

LRMS (Thermospray): 204.2 (MH^+)

(c) Benzo(1,3)dioxol-5-yl-oxo-acetic acid ethyl ester

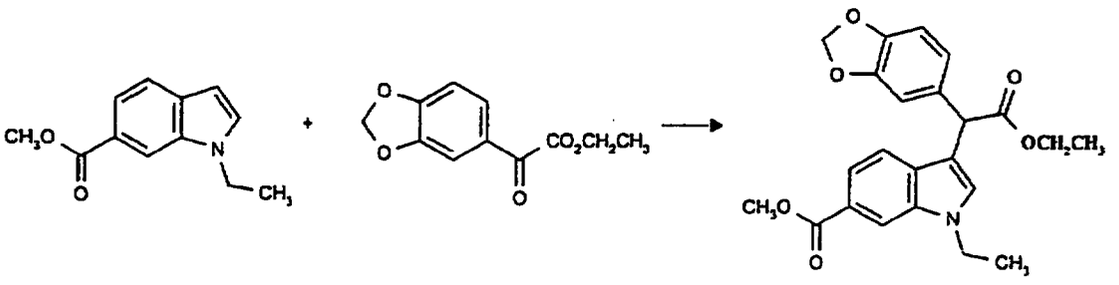


A mixture of ethyl oxalyl chloride (50ml, 0.45mmol) and 1,3-benzodioxole (50g, 0.41 mmol) in dichloromethane (40ml) was added dropwise to a stirred slurry of aluminium trichloride (71g, 0.53mmol) in dichloromethane (500ml) at 0°C under a nitrogen atmosphere. After 2 hours the mixture was poured into iced water and the organic layer was washed with further volumes of water (3 x 500ml), saturated sodium bicarbonate solution (500ml) and brine (500ml). The organic layer was dried (magnesium sulphate) and concentrated to give an orange oil. Flash column chromatography (90% hexane, 10% ethyl acetate) gave 30g of the subtitle compound as a pale yellow oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.40 (t, 3H), 4.40 (q, 2H), 6.10 (s, 2H), 6.85 (d, 1H), 7.50 (s, 1H), 7.60 (d, 1H).

LRMS (Thermospray): 240 (MNH_4^+)

(d) Ethyl 2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl) acetate



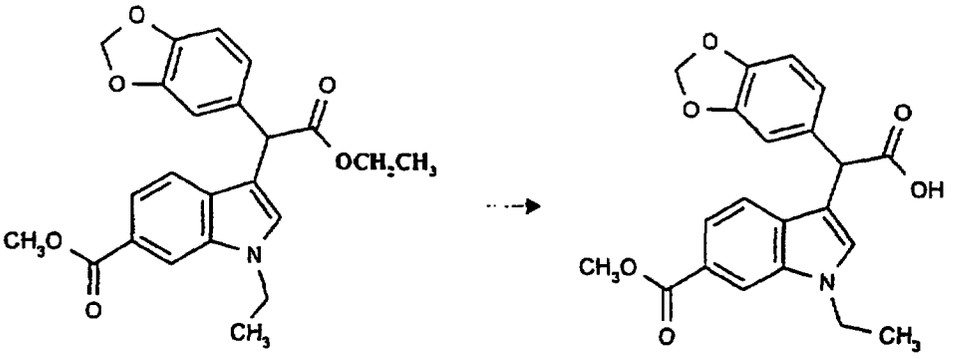
A mixture of 6-methoxycarbonyl-1-ethylindole [the compound of step (b), 2.1g, 10.3mmol] and benzo(1,3)dioxol-5-yl-oxo-acetic acid ethyl ester [the subtitle compound of step (c), 2.4g, 10.9mmol] in dichloromethane (10ml) was added dropwise to a solution of triethylsilane (6.4ml, 51.5mmol) and boron trifluoride diethyletherate (3.28ml, 20.6mmol) in dichloromethane (15ml) at -78°C under a nitrogen atmosphere. After 1 hour the deeply coloured mixture was warmed to -40°C. After 10 hours the mixture was warmed to room temperature and poured into sodium hydroxide solution (200ml of 1M). The flask was washed with dichloromethane (150ml) and the 2 phases were vigorously shaken. The organic layer was separated and washed with brine before drying ($MgSO_4$) and concentrating in vacuo. Flash column chromatography (elution with 90% hexane, 10% ethyl acetate) gave 4.2g of the title compound as a clear oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.45 (t, 3H), 4.00 (s, 3H), 4.25 (q, 2H), 5.15 (s, 1H), 5.90 (s, 2H), 6.70 (d, 1H), 6.80 (d, 1H), 6.85 (s, 1H), 7.30 (s, 1H), 7.40 (d, 1H), 7.70 (d, 1H), 8.10 (s, 1H)

LRMS (Thermospray): 410.2 (MH^+)

Example 2

2-[3-(1-Ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl)acetic acid



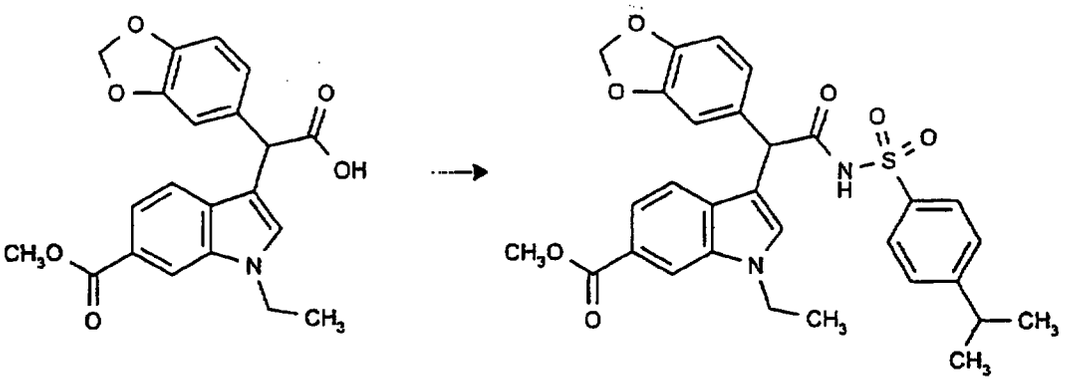
Sodium hydroxide solution (5ml of 2M) was added to a stirred solution of ethyl 2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3.4-methylenedioxyphenyl)acetate [the title compound of Example 1. 3.76g. 9.2mmol] in a 2:1 mixture of tetrahydrofuran and methanol (30ml) at room temperature. The mixture was heated at reflux for 6 hours. following closely by tlc. before recooling and removing the organic solvents in vacuo. The residue was poured into sodium hydroxide solution (200ml of 0.5M) and extracted with dichloromethane to recover any unreacted starting material. The aqueous layer was then acidified to pH1 with 2M hydrochloric acid and extracted with dichloromethane (2 x 300ml). The organic fractions were combined. dried and concentrated in vacuo to give the crude product as an oil. Flash column chromatography (elution with 94% dichloromethane, 5% methanol. 1% ammonia) gave the title compound as a clear oil.

^{1}H NMR (300MHz. $CDCl_3$): δ = 1.45 (t, 3H), 3.95 (s, 3H), 4.20 (q, 2H). 5.20 (s, 1H), 5.95 (s, 2H), 6.80 (d, 1H). 6.85 (d. 1H), 6.90 (s, 1H), 7.35 (s. 1H). 7.40 (d. 1H). 7.85 (d. 1H). 8.10 (s, 1H)

LRMS (Thermospray): 382.6 (MH^+)

Example 3

N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide



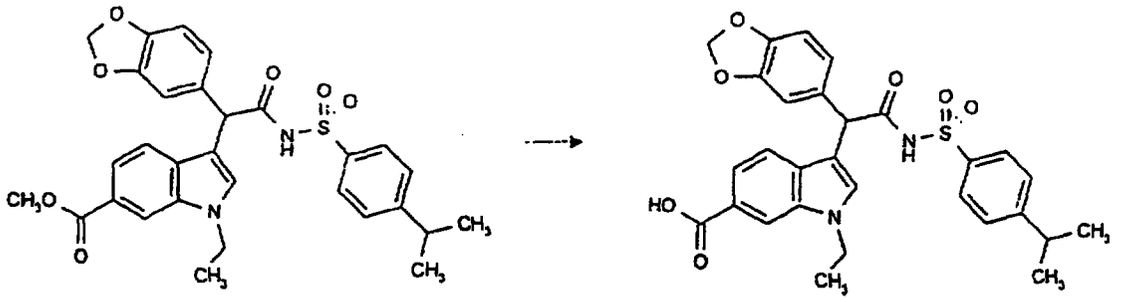
N,N-Carbonyl diimidazole (0.99g, 6.14 mmol) was added to a stirred solution of 2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl)acetic acid [the title compound of Example 2, 1.8g, 4.7mmol] in dichloromethane (60 ml) at room temperature under a nitrogen atmosphere. The solution was heated to reflux for 12 hours. The mixture was cooled and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.92 ml, 6.14mmol) and 4-iso-propylbenzenesulphonamide (1.03g, 5.17mmol) were added. The mixture was refluxed for a further 12 hours. After cooling the mixture was poured into ammonium chloride solution (200ml) and extracted into dichloromethane. The organic fractions were dried ($MgSO_4$) and concentrated to give a yellow oil. Flash column chromatography using firstly dichloromethane and then 3% methanol in dichloromethane gave 1.95g of the title compound as a pale yellow oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.30 (d, 6H), 1.45 (t, 3H), 3.00 (m, 1H), 3.95 (s, 3H), 4.20 (q, 2H), 5.00 (s, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.70 (d, 2H), 7.05 (s, 1H), 7.10 (d, 1H), 7.35 (d, 2H), 7.65 (d, 1H), 7.80 (d, 2H), 8.10 (s, 1H), 8.20 (brs, 1H)

LRMS (Thermospray): 580.4 (MNH_4^+)

Example 4

N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-carboxy)indolyl]-2-(3,4-methylene-dioxyphenyl)acetamide



Aqueous KOH (14.2 ml of a 1M solution) was added to a stirred solution of N-(4-iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylene-dioxyphenyl)acetamide [the title compound of Example 3, 2g, 3.56 mmol] in methanol (50 ml) and the solution was heated at reflux for 8 hours. After cooling the methanol was removed in vacuo and the resulting solution was partitioned between 1M hydrochloric acid (100ml) and dichloromethane (3x100ml). The organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid. Flash column chromatography (using 95% dichloromethane/5% methanol as eluant) gave the title compound as a white solid.

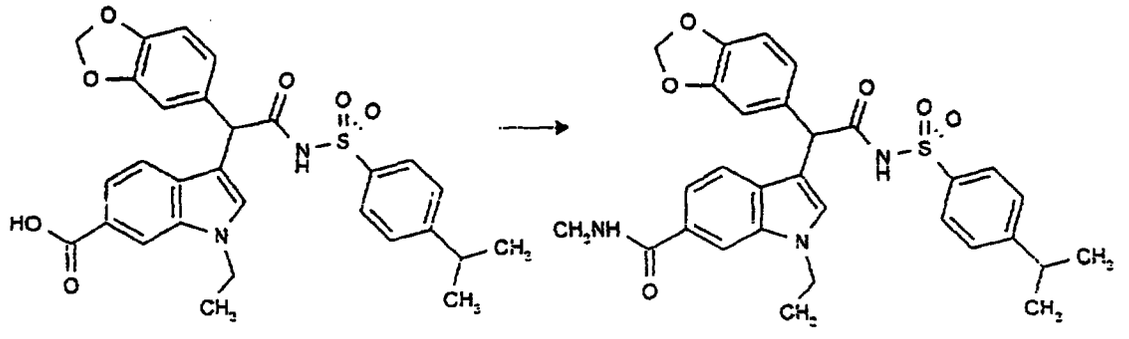
^{1}H NMR (300MHz, $CDCl_3$): δ = 1.25 (d, 6H), 1.40 (t, 3H), 3.00 (m, 1H), 4.15 (q, 2H), 5.00 (s, 1H), 5.90 (s, 2H), 6.65 (d, 2H), 6.70 (s, 1H), 7.00 (s, 1H), 7.15 (m, 1H), 7.30 (d, 2H), 7.60 (m, 1H), 7.85 (d, 2H), 8.10 (s, 1H)

LRMS (Thermospray): 566.3 (MNH_4^+)

Analysis: Found C, 63.29; H, 5.21; N, 4.95. $C_{29}H_{28}N_2O_7S$ requires: C, 63.49; H, 5.14; N, 5.11.

Example 5

N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-methylamido)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (56mg. 0.294mmol) was added to a stirred solution of N-(4-iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-carboxy)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide (the title compound of Example 4. 124mg. 0.23 mmol). hydroxybenzotriazole (37mg. 0.27mmol). triethylamine (63µl. 0.45mmol) and methylamine hydrochloride (23mg. 0.34mmol) in dichloromethane (7ml) at room temperature under a nitrogen atmosphere. After 12 hours the reaction mixture was poured into aqueous sodium hydrogen carbonate solution and extracted with dichloromethane (3 x 100ml). The combined organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid. Flash column chromatography (using ethyl acetate as eluant) gave the title compound as a yellow solid.

^{1}H NMR (300MHz. $CDCl_3$): δ = 1.25 (d. 6H). 1.40 (t. 3H). 3.00 (m. 1H). 3.05 (d. 3H). 4.05 (q, 2H). 5.00 (s. 1H). 5.90 (s. 2H). 6.30 (d. 1H). 6.65 (d. 1H). 6.70 (s. 1H). 6.90 (d, 1H), 6.95 (s, 1H). 7.10 (d. 1H). 7.25 (s, 1H). 7.30 (d. 2H). 7.85 (d. 2H). 7.90 (s. 1H). 9.40 (brs, 1H).

LRMS (Thermospray): 562 (MH^+).

Examples 6-10 were prepared by the method of Example 5. using the product of Example 4 and the appropriate substituted amine starting materials. Their physical data are shown in Table 1.

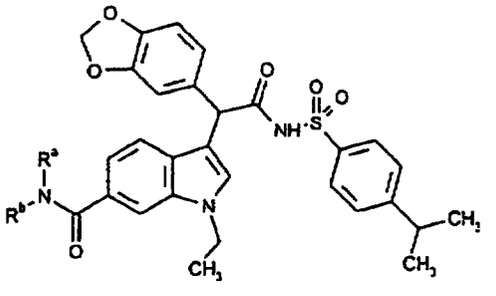
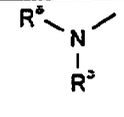
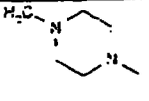
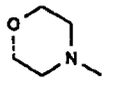
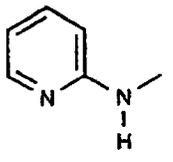
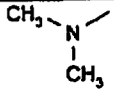
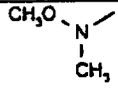


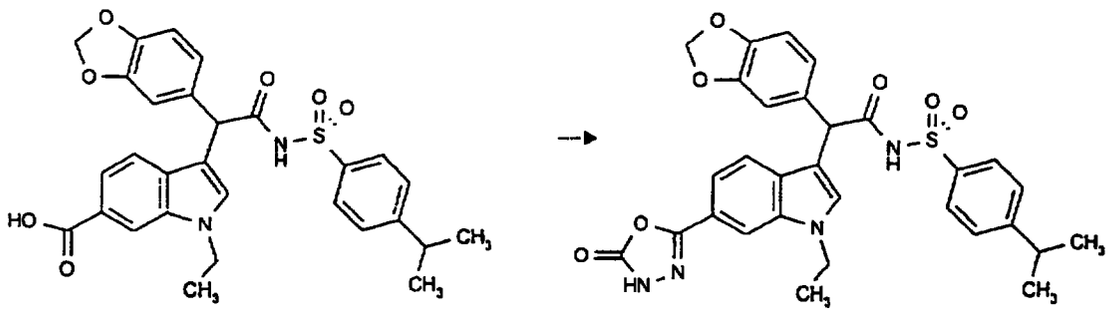
Table 1

Example N°		Physical Data
6		**^{1}H NMR** (300MHz. $CDCl_3$): δ = 1.25 (d. 6H). 1.35 (t. 3H). 2.30 (s. 3H). 2.40 (m. 4H). 2.95 (m. 1H). 3.50 (m. 2H), 4.00 (m. 2H). 4.20 (q. 2H). 5.00 (s. 1H). 5.95 (s.

		2H). 6.65 (d. 2H). 6.70 (s. 1H). 6.85 (d. 1H). 7.00 (m. 1H). 7.20 (m. 3H). 7.40 (s. 1H). 7.80 (d. 2H). LRMS (Thermospray): 631.5 (MH^-)
7		^{1}H NMR (300MHz. $CDCl_3$): δ = 1.25 (d. 6H). 1.40 (t. 3H), 3.00 (m. 1H), 3.70 (m. 8H), 4.10 (q. 2H). 4.90 (s. 1H). 5.90 (s. 2H). 6.60 (s, 1H), 6.70 (m. 2H). 6.95 (m. 3H), 7.30 (d. 2H), 7.40 (s. 1H), 7.80 (d. 2H). 8.85 (brs, 1H) LRMS (Thermospray): 618 (MH^+)
8		^{1}H NMR (300MHz, CD_3OD): δ = 1.25 (d. 6H), 1.40 (t. 3H), 3.00 (m. 1H), 4.20 (q, 2H), 5.10 (s. 1H), 5.80 (s. 2H), 6.70 (d, 2H), 6.75 (s, 1H), 7.00 (s. 1H), 7.15 (m, 1H), 7.30 (d. 1H), 7.40 (d, 2H), 7.50 (d. 1H). 7.75 (m. 1H), 7.80 (d, 2H), 8.05 (s, 1H), 8.20 (d. 1H), 8.35 (m, 1H) LRMS (Thermospray): m/z =625.3 (MH^+)
9		^{1}H NMR (300MHz, CD_3OD): δ = 1.25 (d, 6H), 1.40 (t, 3H), 3.00 (m, 1H), 3.30 (s, 6H), 4.20 (q, 2H), 5.10 (s. 1H), 5.95 (s, 2H), 6.60 (s, 1H), 6.65 (s, 2H). 6.90 (s, 1H). 6.95 (d, 1H), 7.20 (d, 1H), 7.40 (d. 2H), 7.45 (s. 1H), 7.80 (d, 2H) LRMS (Thermospray): 576.6 (MH^+)
10		^{1}H NMR (300MHz, $CDCl_3$): δ = 1.25 (d. 6H), 1.40 (t. 3H), 3.00 (m, 1H). 3.40 (s, 3H). 3.60 (s. 3H). 4.10 (q, 2H). 5.00 (s. 1H), 5.90 (s, 2H). 6.65 (d. 2H), 6.70 (s. 1H), 7.00 (s, 1H). 7.25 (m. 2H). 7.30 (d. 2H), 7.75 (s. 1H), 7.80 (d, 2H) LRMS (Thermospray): 609.5 (MNH_4^-)

Example 11

N-(4-Iso-propylbenzenesulphonyl)-2-[3-[1-ethyl-6-(1,3,4-oxadiazol-2(3H)-one)]indolyl]-2-(3,4-methylenedioxyphenyl)acetamide



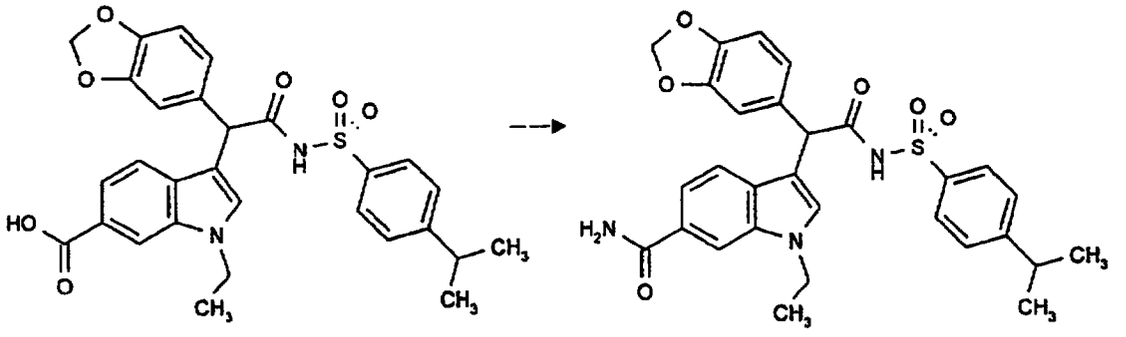
Oxalyl chloride (0.065 ml. 0.74mmol) was added to a stirred solution of N-(4-iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-carboxy)indolyl]-2-(3.4-methylenedioxyphenyl)-acetamide (the compound of Example 4, 340mg, 0.62mmol) in dry tetrahydrofuran (10ml) at room temperature under a nitrogen atmosphere. Dimethylformamide (3 drops) was added and stirring was continued at room temperature for 2 hours. The solvent was removed in vacuo (azeotroping twice with toluene) and the residue redissolved in tetrahydrofuran (5ml). This solution was added to a stirred solution of tert-butylcarbazate (163mg, 1.24 mmol) in tetrahydrofuran (5ml) at room temperature under a nitrogen atmosphere. After 18 hours the solvent was removed in vacuo and the residue dissolved in dichloromethane (3ml). The solution was passed through a short plug of silica washing with 20ml of a 95/5 mixture of dichloromethane/methanol. The solvent was again removed in vacuo and the residue redissolved in tetrahydrofuran (8ml). Concentrated hydrochloric acid (1.9ml) and water (0.6ml) were added and the mixture was heated on a steam bath for 1 hour. After cooling the mixture was poured into water (100ml), the pH adjusted to pH 6 and the product extracted with dichloromethane (2 x 100ml). The organic layers were dried ($MgSO_4$) and concentrated. The yellow residue was redissolved in tetrahydrofuran (8ml) and N,N-carbonyl diimidazolyl (121mg, 0.74mmol) and triethylamine (0.095ml, 0.68mmol) were added. After 18 hours the solution was poured into aqueous ammonium chloride (100ml) and extracted with dichloromethane (2 x 100ml). The organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Flash column chromatography (eluting with 97% dichloromethane, 3% methanol) gave the title compound as a yellow foam.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.25 (d, 6H), 1.45 (t, 3H), 3.00 (m, 1H), 4.10 (q, 2H), 5.00 (s, 1H), 5.90 (s, 2H), 6.65 (s, 1H), 6.70 (d, 1H), 7.00 (s, 1H), 7.20 (d, 1H), 7.40 (d, 1H), 7.40 (d, 2H), 7.45 (d, 1H), 7.80 (s, 1H), 7.90 (d, 2H), 8.40 (s, 1H), 8.60 (s, 1H)

LRMS (Thermospray): 606.4 (MNH_4^+)

Example 12

N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-amido)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide



N,N'-carbonyldiimidazole (98mg, 0.60mmol) was added to a stirred solution of N-(4-iso-propylbenzenesulphonyl)-2-[3-(1-ethyl-6-carboxy)indolyl]-2-(3,4-methylenedioxyphenyl) acetamide (the title compound of Example 4, 300mg, 0.55 mmol), in dry tetrahydrofuran (8ml) under nitrogen. The solution was heated to reflux for 12 hours then cooled to room temperature. Ammonia (gas) was bubbled through the solution for 10 minutes and the flask was securely stoppered and stirring continued for a further 48 hours during which time a yellow precipitate formed. The solvent was removed in vacuo and the residue dissolved in dichloromethane (50ml) the organic layer was washed with aqueous ammonium chloride and then brine before drying (magnesium sulphate) and concentrating in vacuo. The yellow residue was triturated with 5% methanol and 95% dichloromethane to give the product as a pale yellow solid.

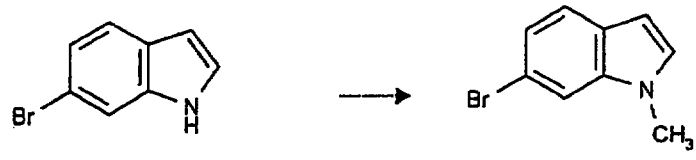
^{1}H NMR (400MHz, CD_3OD): δ = 1.25 (d, 6H), 1.40 (t, 3H), 3.00 (sep, 1H), 4.20 (q, 2H), 5.05 (s, 1H), 5.90 (s, 1H), 6.65 (s, 1H), 6.70 (s, 2H), 7.00 (s, 1H), 7.20 (d, 1H), 7.40 (d, 2H), 7.45 (d, 1H), 7.80 (d, 2H), 8.00 (s, 1H).

LRMS (Thermospray): 548.0 (MH^+).

Example 13

N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-methyl-6-carboxy)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide

(a) 6-Bromo-1-methylindole

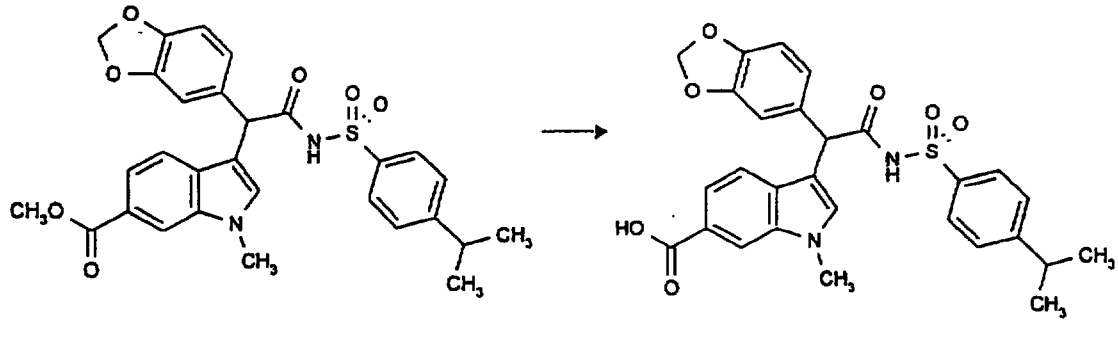


Sodium hydride (4.10g of a 60% dispersion in paraffin wax) was added to a stirred solution of 6-bromoindole (10g, 51.3mmol) in tetrahydrofuran (100ml) at 0°C under a nitrogen atmosphere. After 1 hour iodomethane (6.38ml, 102.6 mmol) was added and the cooling bath removed. After 12 hours methanol was added dropwise until effervescence ceased and then the solvent was removed in vacuo. The thick residue was diluted with dichloromethane and washed first with water then with brine. The organic layer was dried (magnesium sulphate) and concentrated in vacuo to give a dark yellow oil. Filtration through a plug of silica with 90% hexane/10% ethyl acetate as eluant gave the subtitle compound as a pale yellow oil (10.5g).

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.75 (d, 3H), 6.40 (d, 1H), 7.00 (d, 1H), 7.20 (d, 1H), 7.50 (d, 1H), 7.45 (s, 1H).

LRMS (Thermospray): 209.7 (MH^+)

(b) N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-methyl-6-carboxy)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide



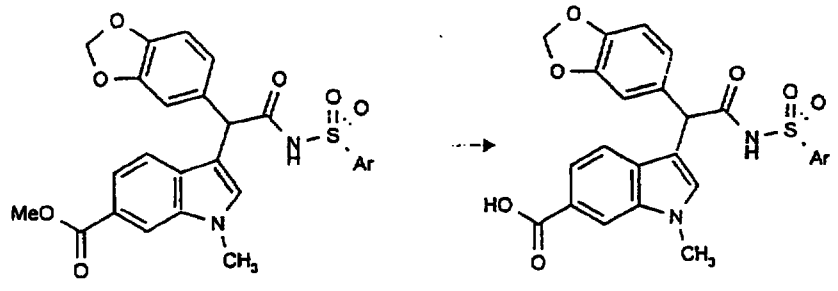
N-(4-Iso-propylbenzenesulphonyl)-2-[3-(1-methyl-6-methoxycarbonyl)indolyl]-2-(3,4-methylenedioxyphenyl)acetamide was prepared by the methods of Examples 1(b), 1(d), 2 and 3, but starting with the subtitle compound of step (a) in place of 6-bromo-1-ethylindole. Then, aqueous KOH (7.3 ml of a 1M solution) was added to a stirred solution of this product (2g, 3.65 mmol) in methanol (50 ml) and the solution was heated at reflux for 8 hours. After cooling the methanol was removed in vacuo and the resulting solution was partitioned between 1M hydrochloric acid (100ml) and dichloromethane (3x100ml).

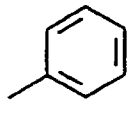
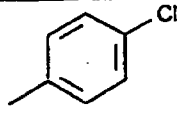
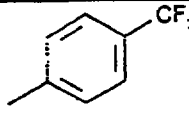
The organic fractions were dried ($MgSO_4$) and concentrated to give a yellow solid. Flash column chromatography (using 95% dichloromethane/5% methanol as eluant) gave the title compound as a white solid (1.44g).

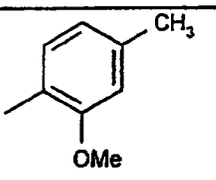
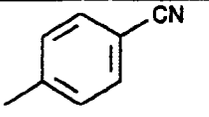
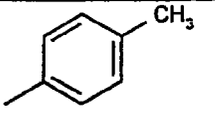
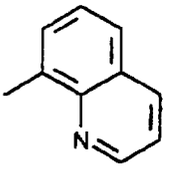
^{1}H NMR (400MHz. $CDCl_3$): δ = 1.25 (d. 6H). 3.00 (hept. 1H). 3.80 (s. 3H). 5.05 (s, 1H). 5.95 (s, 2H). 6.65 (d, 2H). 6.70 (s. 1H). 7.00 (s. 1H). 7.20 (d. 1H). 7.40 (d, 2H). 7.65 (d, 1H). 7.90 (d. 2H). 8.05 (s. 1H).

LRMS (Thermospray): 552.7 (MNH_4^+)

Examples 14-18 were prepared using the method of Example 13(b). but using the appropriate aromatic sulphonamide in place of 4-isopropylbenzenesulphonamide in the method of Example 3.

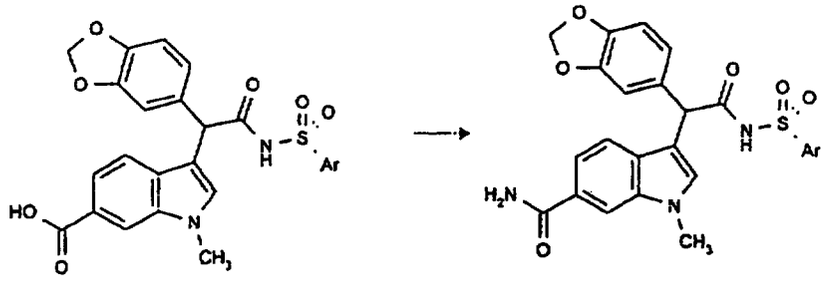


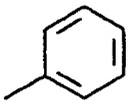
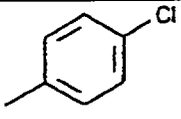
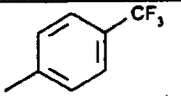
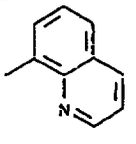
Example N°	Ar	Physical Data
14		**^{1}H NMR** (300MHz. $CDCl_3$): δ = 3.80 (s. 3H). 5.00 (s, 1H), 5.90 (s, 2H), 6.60 (s. 1H), 6.65 (d, 2H), 7.00 (s, 1H), 7.10 (d. 1H), 7.45 (m 2H), 7.60 (m, 2H), 7.90 (d, 2H), 8.00 (s, 1H), 8.80 (brs, 1H). **LRMS** (Thermospray): 493.1 (MH^+).
15		**^{1}H NMR** (400MHz. $CDCl_3$): δ = 3.80 (s. 3H). 5.00 (s. 1H), 6.00 (s. 2H). 6.65 (m. 3H), 7.00 (s, 1H). 7.20 (d, 1H), 7.50 (d. 2H). 7.70 (d. 1H). 7.90 (d. 2H). 8.05 (s. 1H). 8.45 (brs, 1H). **LRMS** (APCI): 527.0. 527.8 (MH^+).
16		**^{1}H NMR** (400MHz. $CDCl_3$): δ = 3.80 (s. 3H). 5.00 (s. 1H). 5.90 (s. 2H). 6.65 (m. 3H). 7.00 (s.

		1H). 7.20 (d. 1H). 7.65 (d. 1H). 7.80 (d. 2H). 8.00 (s. 1H). 8.10 (d, 2H). 9.00 (s. 1H). **LRMS** (APCI): 592.9 (MNH_4^+).
17*		**^{1}H NMR** (400MHz. $CDCl_3$): δ = 2.40 (s. 3H), 3.40 (s. 3H). 3.75 (s. 3H). 5.05 (s. 1H). 5.90 (d, 2H), 6.45 (s. 1H), 6.70 (d. 1H). 6.75 (d, 1H), 6.85 (d. 1H). 7.10 (s. 1H). 7.30 (m. 3H). 7.60 (d, 1H), 7.90 (d. 1H). 8.00 (s. 1H), 9.20 (brs. 1H). **LRMS** (APCI): 537.0 (MH^+).
18		**^{1}H NMR** (300MHz. CD_3OD): δ = 3.75 (s, 3H), 4.95 (s. 1H). 5.95 (d. 2H). 6.65 (s. 1H). 6.75 (s, 2H). 7.15 (s. 1H). 7.25 (d. 1H). 7.65 (d. 1H), 7.95 (d, 2H). 8.05 (d. 2H), 8.10 (s. 1H). **LRMS** (APCI): 518.3 (MH^+).
19		**^{1}H NMR** (300MHz. $CDCl_3$): δ = 2.45 (s, 3H), 3.80 (s. 3H). 5.00 (s. 1H), 5.95 (s. 2H). 6.65 (m, 3H), 7.00 (s. 1H). 7.15 (d. 1H), 7.30 (d, 2H), 7.60 (d. 1H), 7.80 (d. 2H). 8.00 (s, 1H), 8.70 (s, 1H). **LRMS** (APCI): 507.3 (MH^+).
20		**^{1}H NMR** (300MHz. d_6-DMSO): δ = 3.64 (s. 3H), 5.23 (s, 1H). 5.92 (s. 2H), 6.52 (s. 1H), 6.60 (d, 1H). 6.68 (d. 1H). 6.90 (s, 1H). 7.03 (d. 1H), 7.35 (d. 1H). 7.60 (dd. 1H). 7.75 (dd. 1H). 7.90 (s, 1H). 8.30 (d. 1H). 8.40 (d. 1H), 8.49 (d. 1H), 8.80 (d. 1H). **LRMS** (APCI): 543.8 (MH^-) **m.p.**: 238-240°C dec.

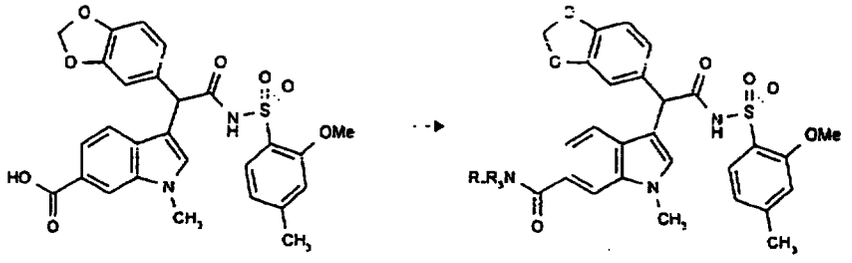
* See Preparation 11 for preparation of aromatic sulphonamide

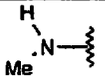
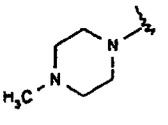
Examples 21-24 were prepared by the method of Example 12 from the compounds of Examples 14. 15. 16 and 20 respectively.



Example N°	Ar	Physical Data
21		**^{1}H NMR** (400MHz, CD_3OD): δ = 3.70 (s, 3H), 5.05 (s, 1H), 5.80 (s, 2H), 6.80 (m, 3H), 6.85 (s, 1H), 7.20 (m, 2H), 7.40 (m, 3H), 7.90 (m, 3H). **LRMS** (APCI): 492 (MH^+).
22		**^{1}H NMR** (400MHz, CD_3OD): δ = 3.65 (s, 3H), 5.05 (s, 1H), 5.80 (d, 2H), 6.85 (m, 3H), 6.95 (s, 1H), 7.20 (d, 1H), 7.40 (d, 2H), 7.45 (d, 1H), 7.80 (d, 2H), 7.95 (s, 1H). **LRMS** (APCI): 525.9, 526.7 (MH^+).
23		**^{1}H NMR** (300MHz, CD_3OD): δ = 3.70 (s, 3H), 5.00 (s, 1H), 5.80 (s, 2H), 6.60 (d, 1H), 6.70 (s, 1H), 6.75 (d, 1H), 7.00 (s, 1H), 7.30 (d, 1H), 7.40 (d, 1H), 7.65 (d, 2H), 7.90 (s, 1H), 8.00 (d, 2H). **LRMS** (APCI): 560.9 (MH^+).
24		**^{1}H NMR** (400MHz, d_6-DMSO): δ = 3.64 (s, 3H), 4.87 (s, 1H), 5.90 (d, 2H), 6.64 (d, 1H), 6.65 (d, 1H), 6.76 (s, 1H), 7.02 (s, 1H), 7.09 (brs, 1H), 7.20 (d, 1H), 7.35 (d, 1H), 7.55 (dd, 1H), 7.60 (dd, 1H), 7.78 (brs, 1H), 7.90 (s, 1H), 8.08 (d, 1H), 8.29 (d, 1H), 8.39 (d, 1H), 8.90 (d, 1H). **Analysis**: Found: C, 57.98; H, 4.62; N, 11.58. $C_{28}H_{22}N_4O_6S$; NH_3; H_2O: Requires: C, 58.22; H, 4.71; N, 12.12.

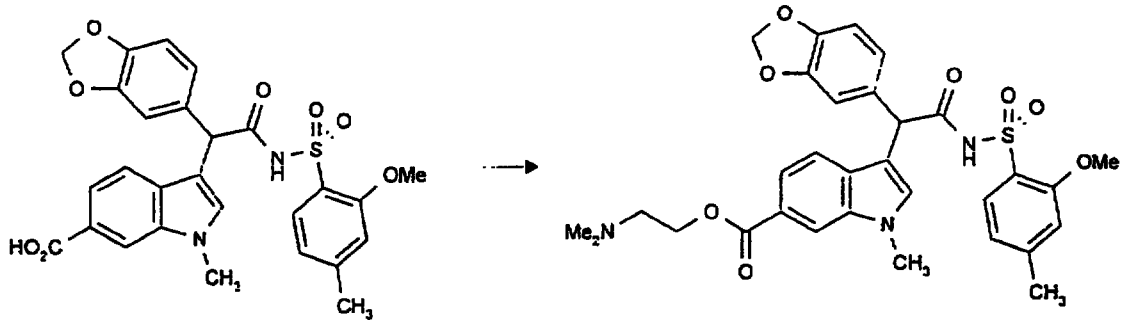
Examples 25-26 were prepared by the method of Example 5 from the compound of Example 17 and the appropriate amine.



Example N°	R_7R_8N	Physical Data
25		**^{1}H NMR** (400MHz. d_6-DMSO): δ = 2.70 (s, 3H). 2.80 (d. 3H). 3.60 (s. 3H). 3.80 (s. 3H), 5.20 (s, 1H). 5.95 (s. 2H), 6.70 (d. 1H). 6.75 (s. 1H), 6.80 (d, 1H). 6.95 (s. 1H). 7.05 (s, 1H). 7.20 (d, 1H). 7.40 (d, 1H). 7.65 (d, 1H). 7.90 (s. 1H). 8.25 (s, 1H), 12.3 (brs. 1H). **LRMS** (APCI): 550.4 (MH^+).
26		**^{1}H NMR** (400MHz, CD_3OD): δ = 2.45 (s, 3H), 2.50 (s, 3H). 2.60 (brs. 4H). 3.65 (s. 3H). 3.70 (brs. 4H), 3.80 (s. 3H). 5.15 (s. 1H). 5.90 (s, 2H). 6.70 (s, 1H). 6.80 (m. 2H). 6.95 (s, 1H). 7.00 (d, 1H), 7.05 (s. 1H). 7.10 (d. 1H). 7.40 (d. 1H). 7.55 (s, 1H). 7.85 (d. 1H). **LRMS** (APCI): 619.9 (MH^+).

Example 27

2-(Dimethylamino)ethyl 3-[1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl]-1-methyl-1*H*-6-indolecarboxylate



1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (128mg, 0.67mmol) was added to a stirred solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolecarboxylic acid (the product of Example 17, 300mg, 0.56 mmol), N,N-dimethylaminopyridine (75mg, 0.61mmol) and dimethylaminoethanol (0.17ml, 1.67mmol) in a mixture of CH_2Cl_2 (9ml) and DMF (0.5ml) at room temperature under a nitrogen atmosphere. After 12h a fine white precipitate had formed. The product was removed by filtration and washed with cold methanol.

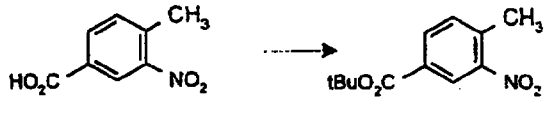
^{1}H NMR (400MHz, d_6-DMSO): δ = 2.40 (s, 9H), 2.70 (t, 2H), 3.60 (s, 3H), 3.75 (s, 3H), 4.30 (t, 2H), 5.05 (s, 1H), 5.90 (s, 2H), 6.65 (d, 1H), 6.70 (s, 1H), 6.75 (d, 1H), 6.80 (d, 1H), 6.85 (s, 1H), 7.20 (s, 1H), 7.30 (d, 1H), 7.50 (d, 1H), 7.60 (d, 1H), 8.00 (s, 1H).

LRMS (APCI): 608.9 (MH^+).

Example 28

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolecarboxamide

(a) 3-Nitro-4-methylbenzoic acid tert-butyl ester



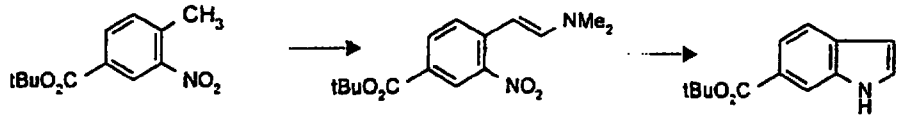
To a solution of 3-nitro-4-methylbenzoic acid (17.3g 96mmol) in dichloromethane (250ml) and tert-butanol (35.8g 470mmol) at 0°C under nitrogen was added 4-dimethylaminopyridine (6g 50mmol) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (25.8g 140mmol) and the solution allowed to come to room temperature over 1 hour, then stirred overnight. The solution was poured into 1:1 ethyl acetate : water

(800ml each) and the organic layer washed with aqueous bicarbonate and saturated aqueous sodium chloride. then dried ($MgSO_4$) and evaporated. to give the product as a clear oil (22.6g).

^{1}H NMR (300MHz $CDCl_3$): 1.60 (s. 9H). 2.65 (s. 3H). 7.40 (d. 1H) 8.10 (d. 1H). 8.55 (s. 1H).

LRMS (Thermospray): 238.4 (MH^-)

(b) Indole 6- tert-butyl ester

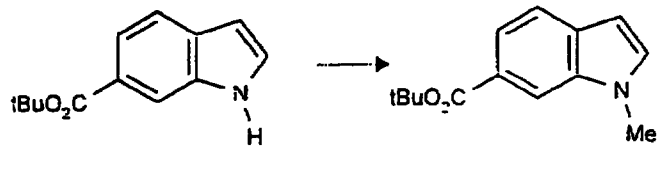


To a solution of the ester from step (a) (23g 97mmol) in dimethylformamide (100ml) was added dimethylformamidedimethyl acetal (50ml) and pyrrolidine (20 drops). The solution was stirred under nitrogen at 80°C overnight to give a dark red solution, which was evaporated to dryness to give a dark red oil. which crystallised on standing and was used without further purification.

The crude dimethyl enamine (assumed 97mmol) was dissolved in toluene (850ml) and hydrogenated overnight at a pressure of 345 kPa (50psi) in the presence of 10% palladium-on-charcoal (5g). Catalyst was removed by filtration and solvents evaporated. The residue was chromatographed on flash silica using dichloromethane eluant to give product as a crystalline solid (12.6g).

^{1}H NMR (400MHz $CDCl_3$): 1.65 (s. 9H). 6.60 (s. 1H). 7.40 (t. 1H), 7.65 (d. 1H), 7.80 (d. 1H), 8.15 (s, 1H). 8.50 (s. 1H).

(c) 1-Methylindole 6-tert-butyl ester



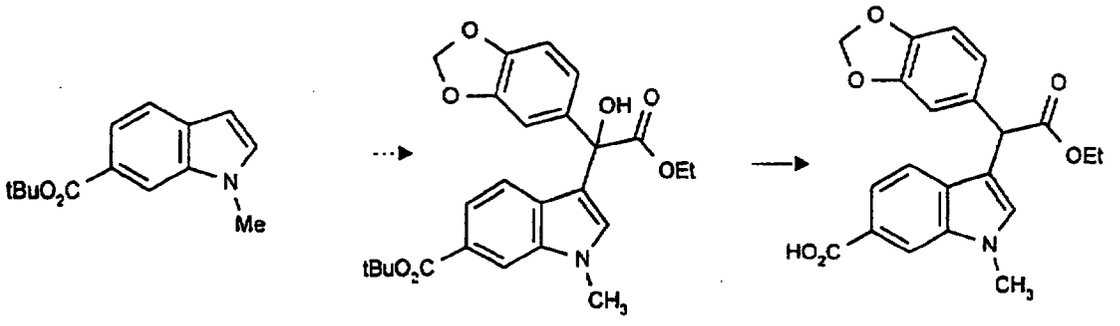
To a solution of the indole from step (b) (12.5g 57mmol) in tetrahydrofuran (150ml) at 0°C under nitrogen was added sodium hydride as a 60% suspension in oil (2.28g 57mmol). When effervescence ceased. methyl iodide (3.6ml 57mmol) was added and the solution

allowed to come to room temperature. The mixture was stirred for 1 hour. poured into ethyl acetate (500ml). and washed with water and saturated brine. then dried ($MgSO_4$) and evaporated to give an oil which was contaminated with hydride oil. but sufficiently pure to continue (14.1g).

^{1}H NMR (300MHz $CDCl_3$): 1.65 (s. 9H). 3.85 (s. 3H). 6.50 (d. 1H). 7.20 (s. 1H). 7.60 (d. 1H), 7.75 (d. 1H). 8.05 (s. 1H).

LRMS (Thermospray): 232.2 (MH^+)

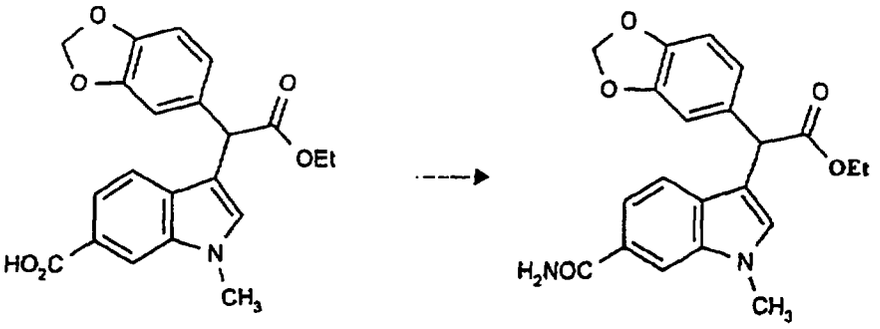
(d) Ethyl 2-[3-(1-methyl-6-carboxy)indolyl]-2-(3,4-methylenedioxyphenyl)acetate



To a solution of boron trifluoride diethyl etherate (14ml 132mmol) and triethysilane (40ml 240mmol) in dichloromethane (60ml) at -78°C under nitrogen was added a solution of the indole from (c) (14g 60mmol) and benzodioxole ethylpyruvate (14g, 66mmol) in dichloromethane (80ml) dropwise. The solution was stirred at -78°C for 30 minutes, then quenched with aqueous hydrochloric acid and the organic layer separated. dried ($MgSO_4$) and evaporated. The hydroxy intermediate was isolated by flash chromatography using 30% ethyl acetate in hexane eluant as a buff solid (19.38g). This intermediate (15g) was dissolved in dichloromethane (50ml) and triethyl silane (15g) at 0°C under nitrogen, and trifluoroacetic acid (50ml) was added dropwise over 10 minutes. After 1 hour at room temperature the reaction was quenched with water. and the organic layer separated. dried ($MgSO_4$) and evaporated. Chromatography on flash silica using ethyl acetate eluant gave the acid ester as a pale foam (9.53g).

^{1}H NMR (400MHz $CDCl_3$): 1.25 (t. 3H). 3.85 (s. 3H). 4.20 (m. 2H), 5.20 (s. 1H). 5.95 (s. 2H). 6.70 - 8.20 (m. 7H).

(e) Ethyl 2-(1,3-Benzodioxol-5-yl)-2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)acetate

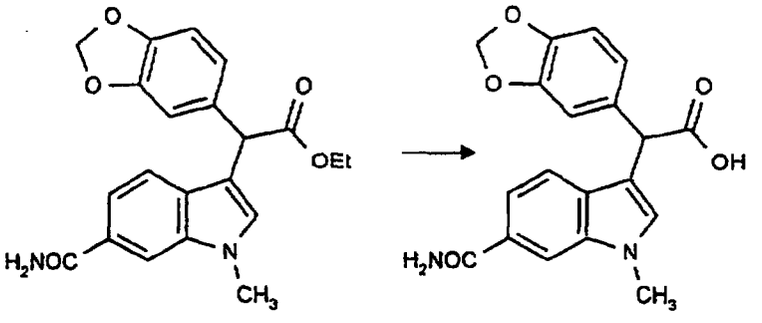


To a solution of the acid (9.43g 25mmol) in tetrahydrofuran (125ml) was added carbonyldiimidazole (4.0g 25mmol) and the solution refluxed for 4 hours. The solution was cooled to 0°C and saturated with gaseous ammonia then stirred overnight. The reaction was concentrated in vacuo and partitioned between ethyl acetate and water. The organic layer was washed twice with water and brine, then dried ($MgSO_4$) and evaporated. Product was isolated by flash chromatography using 2% methanol in dichloromethane eluant to give the amide ester as a pale foam (5.6g).

^{1}H NMR (300MHz d_6-DMSO): 1.20 (t. 3H), 3.80 (s, 3H), 4.15 (q, 2H). 5.20 (s, 1H). 5.95 (d, 2H), 6.80 - 8.00 (m, 9H).

LRMS (Thermospray): 381.1 (MH^+)

(f) 2-(1,3-Benzodioxol-5-yl)-2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)acetic acid

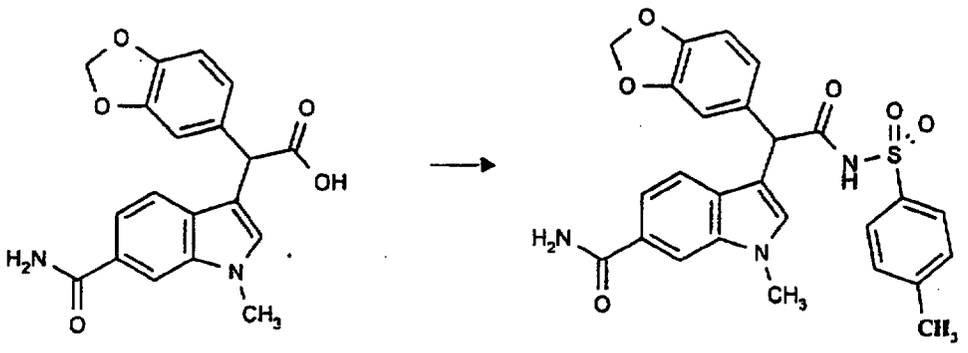


To a solution of the amide ester from step (e) (5.6g 14.7mmol) in tetrahydrofuran (60ml) and methanol (30ml) was added aqueous sodium hydroxide solution (10ml of 5M. 50mmol) dropwise, and the mixture heated at reflux for 9 hours. Solvents were removed in vacuo and the residue dissolved in aqueous sodium hydroxide and washed with dichloromethane. The aqueous layer was acidified with aqueous hydrochloric acid and the product isolated by filtration. Trituration with ethyl acetate gave the product as a white solid (5.1g).

^{1}H NMR (300MHz d_6-DMSO): 3.80 (s. 3H). 5.15 (s. 1H). 6.00 (d. 2H). 6.80 - 8.00 (m. 9H).

LRMS (Thermospray): 353.5 (MH^-)

(g) 3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolecarboxamide

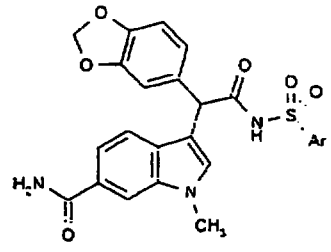


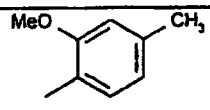
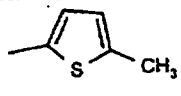
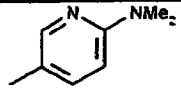
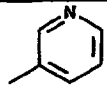
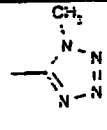
1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (65mg, 0.34mmol) was added to a stirred solution 2-(1,3-benzodioxol-5-yl)-2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)acetic acid (from step (f). 100mg, 0.28 mmol), dimethylaminopyridine (45mg, 0.37mmol) and p-toluenesulphonamide (53mg, 0.31mmol) in dichloromethane (5ml) and dimethylformamide (1ml) at room temperature under a nitrogen atmosphere. After 14h the solvent was removed in vacuo and the product was extracted from 1N hydrochloric acid (50ml) with ethyl acetate (2 x 50ml). The organic layers were dried and concentrated to give a fawn foam. Flash column chromatography (elution with 95% dichloromethane/5% methanol) gave the product (95mg) as a white solid.

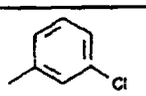
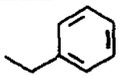
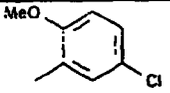
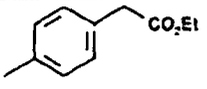
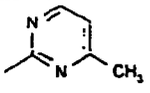
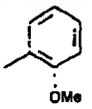
^{1}H NMR (300MHz. CD_3OD): δ = 2.40 (s, 3H). 3.75 (s, 3H), 5.05 (s, 1H), 5.90 (s, 2H). 6.60 (m. 3H). 6.90 (s. 1H). 7.20 (d. 1H). 7.30 (d. 2H). 7.40 (d. 1H). 7.80 (d. 2H). 7.95 (s, 1H).

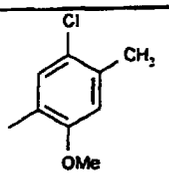
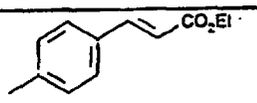
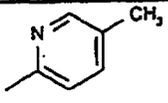
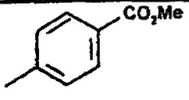
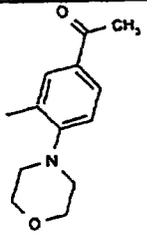
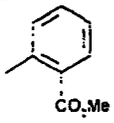
LRMS (APCI): 506 (MH^+).

Examples 29-45 were prepared by reacting the compound of Example 28(f) with the appropriate aromatic sulphonamide using the method of Example 28(g).



Example N°	Ar	Physical Data
29		**^{1}H NMR** (400MHz, d_6-DMSO): δ = 2.35 (s, 3H). 3.60 (s, 3H). 3.75 (s, 3H). 5.20 (s, 1H), 5.95 (d, 2H). 6.60 - 8.00 (m, 12H). **LRMS** (Thermospray) 536.4 (MH^+)
30		**^{1}H NMR** (300MHz, CD_3OD): δ = 2.45 (s, 3H), 3.80 (s, 3H). 5.00 (s, 1H). 5.85 (s, 2H), 6.90 (m, 4H). 7.00 (s, 1H), 7.20 (d, 1H). 7.40 (d, 1H). 7.50 (d, 1H), 7.90 (s, 1H). **LRMS** (APCI): 512.1 (MH^+).
31		**^{1}H NMR** (300MHz, CD_3OD): δ = 3.10 (s, 6H), 3.60 (s, 3H). 5.00 (s, 1H), 5.80 (s, 2H), 6.45 (d, 1H). 6.65 (m, 3H). 7.00 (s, 1H). 7.20 (d, 1H). 7.40 (d, 1H). 7.80 (d, 1H). 7.90 (s, 1H). 8.50 (s, 1H). **LRMS** (APCI): 536.2 (MH^+).
32		**^{1}H NMR** (300MHz, d_6-DMSO): δ = 3.70 (s, 3H). 4.80 (s, 1H). 5.90 (d, 2H). 6.65 (d, 1H). 6.70 (d, 1H). 6.80 (s, 1H). 7.10- 7.40 (m, 5H). 7.90 (s, 1H), 8.00 (d, 1H). 8.50 (d, 1H). 8.80 (s, 1H). **LRMS** (APCI): 493.8 (MH^+).
33		**^{1}H NMR** (400MHz, CD_3OD): δ = 3.80 (s, 3H). 4.00 (s, 3H). 5.00 (s, 1H), 5.80 (s, 2H). 6.70 (d, 1H). 6.80 (m, 2H), 7.20 (m, 4H).

		LRMS (APCI): 498 (MH^+).
34		^{1}H NMR (400MHz, d_6-DMSO): δ = 3.75 (s, 3H), 5.05 (s, 1H), 5.95 (s, 2H), 6.70 (d, 1H), 6.75 (s, 1H), 6.80 (d, 1H), 7.05 (s, 1H), 7.20 (d, 1H), 7.45 (d, 1H), 7.60 (t, 1H), 7.75 (m, 3H), 8.00 (s, 1H). LRMS (Thermospray): 525.7, 527.3 (MH^+).
35		^{1}H NMR (300MHz, $CDCl_3$): 3.85 (s, 3H), 4.70 (s, 2H), 5.15 (s, 1H), 6.00 (s, 2H), 6.80 - 8.00 (m, 14H) 11.95 (s, 1H). LRMS (Thermospray): 505.4 (MH^+)
36		^{1}H NMR (300MHz, d_6-DMSO): 3.65 (s, 3H), 3.75 (s, 3H), 5.20 (s, 1H) 5.95 (d, 2H) 6.60 - 8.00 (m, 12H), 12.60 (s, 1H). LRMS (Thermospray): 555.7 (MH^+)
37		^{1}H NMR (400MHz, $CDCl_3$): δ = 1.10 (t, 3H), 3.55 (s, 2H), 3.60 (s, 3H), 4.00 (q, 2H), 4.80 (s, 1H), 5.75 (s, 2H), 6.60 (s, 3H), 6.80 (s, 1H), 7.00 (d, 1H), 7.25 (m, 3H), 7.75 (s, 1H), 7.80 (d, 2H). LRMS (APCI): 578.5 (MH^+).
38		^{1}H NMR (400MHz, $CDCl_3$): δ = 2.50 (s, 3H), 3.70 (s, 3H), 5.05 (s, 1H), 5.80 (s, 2H), 6.60 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H), 7.00 (s, 1H), 7.05 (d, 1H), 7.10 (d, 1H), 7.25 (d, 1H), 7.85 (s, 1H), 7.90 (d, 1H). LRMS (APCI): 508.0 (MH^+).
39		^{1}H NMR (400MHz, d_6-DMSO): 3.65 (s, 3H), 3.75 (s, 3H), 5.20 (s, 1H), 5.95 (d, 2H), 6.60 - 8.00 (m, 13H), 12.40 (s, 1H).

40‡		^{1}H NMR (400MHz, d_6-DMSO): 2.40 (s, 3H), 3.65 (s, 3H), 3.80 (s, 3H), 5.20 (s, 1H), 5.95 (d, 2H), 6.60 - 8.00 (m, 11H), 12.50 (s, 1H).
41*		^{1}H NMR (400MHz, CD_3OD): δ = 2.45 (t, 3H), 3.75 (s, 3H), 4.35 (q, 2H), 5.15 (s, 1H), 5.95 (s, 2H), 6.80 (m, 4H), 6.95 (s, 1H), 7.35 (d, 1H), 7.55 (d, 1H), 7.75 (d, 2H), 7.80 (s, 1H), 7.95 (d, 2H), 8.00 (s, 1H).
42†		^{1}H NMR (400MHz, d_6-DMSO): δ = 3.40 (s, 3H), 3.80 (s, 3H), 5.20 (s, 1H), 6.00 (s, 2H), 6.70 (d, 1H), 6.75 (s, 1H), 6.80 (d, 1H), 7.00 (s, 1H), 7.20 (m, 2H), 7.45 (d, 1H), 7.80 (m, 2H), 7.95 (s, 1H), 8.45 (s, 1H). LRMS (APCI): 506.7 (MH^+).
43		^{1}H NMR (400MHz, CD_3OD): δ = 3.70 (s, 3H), 3.95 (s, 3H), 5.00 (s, 1H), 5.80 (s, 2H), 6.60 (d, 1H), 6.80 (s, 1H), 6.85 (d, 1H), 7.05 (s, 1H), 7.25 (d, 1H), 7.40 (d, 1H), 7.80 (d, 2H), 7.90 (s, 1H), 7.95 (d, 2H). LRMS (Thermospray): 550.0 (MH^+).
44		^{1}H NMR (400MHz, CD_3OD): δ = 2.70 (m, 2H), 2.75 (s, 3H), 2.85 (m, 2H), 3.75 (m, 4H), 3.95 (s, 3H), 5.25 (s, 1H), 6.00 (d, 2H), 6.80 (m, 3H), 7.10 (s, 1H), 7.40 (d, 1H), 7.50 (d, 1H), 7.60 (d, 1H), 8.05 (s, 1H), 8.30 (d, 1H), 8.80 (s, 1H). LRMS (APCI): 619.9 (MH^+).
45		^{1}H NMR (300MHz, d_6-DMSO): δ = 3.70 (s, 3H), 3.75 (s, 3H), 4.96 (br, 1H), 5.90 (d, 2H), 6.70-6.78 (m, 2H), 6.84 (s, 1H), 7.10 (brs, 1H), 7.22 (s, 1H), 7.32 (d, 1H),7.40-7.60 (m, 4H).

		7.80 (brs. 1H). 7.90-7.95 (m. 2H). 12.50 (brs. 1H exchangeable). **Analysis**: Found: C. 54.90: H. 3.94: N. 6.98. $C_{27}H_{23}N_2O_8S$; 0.6 CH_2Cl_2 Requires: C. 55.20: H. 4.06: N. 7.00.

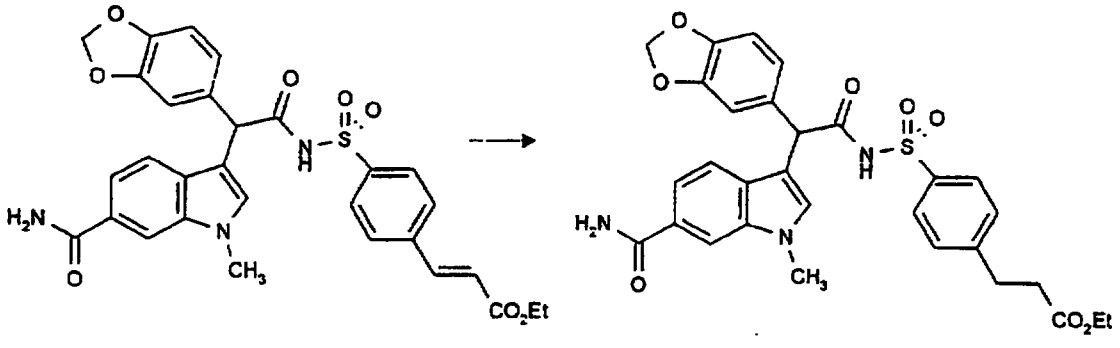
‡ See Preparation 8 for sulphonamide preparation

* See Preparation 3 for sulphonamide preparation

† See Preparation 4 for sulphonamide preparation

Example 46

Ethyl 3-(4-[2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)-2-(1,3-benzodioxol-5-yl)acetyl]sulfamoylphenyl)propanoate



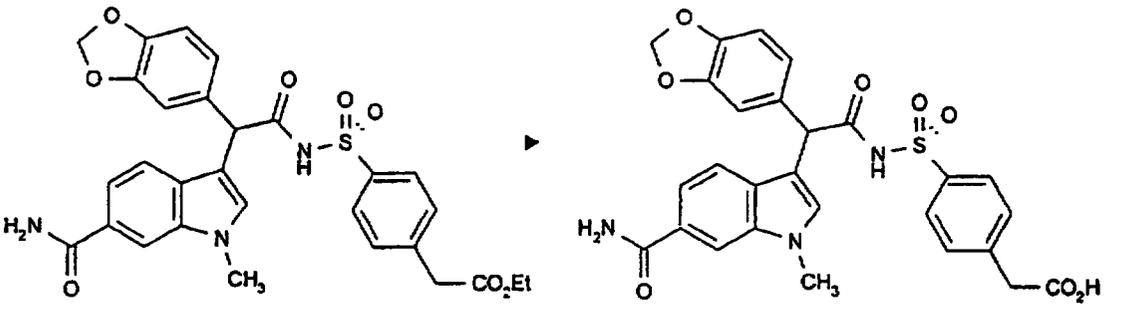
Ethyl (*E*)-3-(4-[2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)-2-(1,3-benzodioxol-5-yl)acetyl] sulfamoylphenyl)-2-propenoate (the compound of Example 41, 0.24g, 0.40mmol) was dissolved in ethanol (5ml) and 5% palladium-on-carbon (24mg) was added. The mixture was placed in a pressure vessel and a hydrogen pressure of 345 kPa (50 psi) was maintained for 48h. The reaction mixture was filtered through Arbocel™ and concentrated in vacuo. Flash column chromatography (elution with 5% methanol/90% dichloromethane) gave the product (70mg).

^{1}H NMR (400MHz, CD_3OD): δ = 1.20 (t, 3H). 2.60 (t, 2H), 3.00 (t, 2H). 3.75 (s, 3H). 4.05 (q, 2H). 5.05 (s, 1H). 5.85 (s, 2H). 6.60 (s, 1H). 6.70 (s, 2H). 6.90 (s, 1H). 7.20 (d, 1H). 7.30 (d, 2H). 7.40 (d, 1H). 7.80 (d, 2H). 7.90 (s, 1H).

LRMS (APCI): 591.9 (MH^-).

Example 47

2-(4-[2-(1,3-Benzodioxol-5-yl)-2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)acetyl]-sulfamoylphenyl)acetic acid

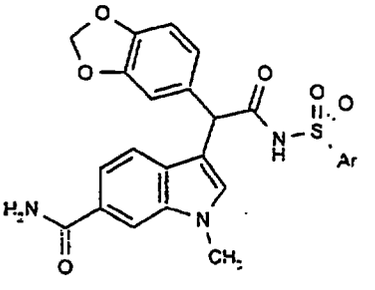


1M Sodium hydroxide solution (0.57ml) was added to a stirred solution of ethyl 2-(4-[2-(1,3-benzodioxol-5-yl)-2-(6-carbamoyl-1-methyl-1*H*-3-indolyl)acetyl]sulfamoylphenyl) acetate (the product of Example 37, 110mg, 0.19mmol) in aqueous dioxan (8ml dioxan:2ml H_2O) at room temperature. After 1h the solvent was removed in vacuo. The reaction mixture was diluted with ethyl acetate and poured into 0.5M hydrochloric acid (50ml) and extracted with ethyl acetate (2 x 50ml). The organic layers were dried (magnesium sulphate) and concentrated in vacuo to give a yellow foam. Flash column chromatography (elution with 95% dichloromethane /5% methanol) gave the product as a white solid (90mg).

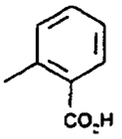
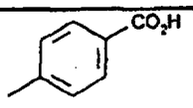
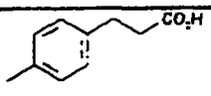
^{1}H NMR (400MHz, $CDCl_3$): δ = 3.40 (s, 2H), 3.90 (s, 3H), 5.20 (s, 1H), 6.00 (s, 2H), 6.80 (m, 3H), 7.00 (s, 1H), 7.30 (d, 1H), 7.60 (d, 2H), 7.65 (s, 1H), 8.00 (s, 1H), 8.10 (d, 2H).

LRMS (APCI): 549.9 (MH^+).

Examples 48-50 were made using the method of Example 47, starting with the compounds of Examples 45, 43 and 46 respectively.



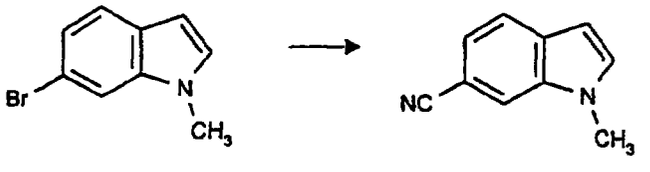
Example N°	Ar	Physical Data

48		^{1}H NMR (300MHz. d_6-DMSO): δ = 3.75 (s. 3H). 5.26 (s. 1H). 5.96 (s. 2H). 6.70-6.82 (m. 3H). 7.10-7.17 (m, 2H). 7.27 (d. 1H). 7.46 (d. 1H). 7.60-7.86 (m. 4H). 7.96 (s. 1H). 8.00 (d, 1H). **LRMS** (APCI): 536.1 (MH^+)
49		^{1}H NMR (400MHz, CD_3OD): δ = 3.80 (s, 3H), 5.05 (s. 1H). 5.80 (d. 2H), 6.60 (s, 1H), 6.70 (d, 1H), 6.75 (d, 1H), 6.90 (s. 1H), 7.20 (d, 1H), 7.40 (d, 1H), 7.85 (s, 1H), 7.90 (d, 2H), 8.00 (d. 2H). **LRMS** (APCI): 536.0 (MH^+).
50		^{1}H NMR (300MHz, CD_3OD): δ = 2.80 (t, 2H), 3.00 (t, 2H), 3.75 (s, 3H), 5.00 (s, 1H), 5.80 (d, 2H), 6.60 (m, 3H), 6.90 (s. 1H), 7.20 (d, 1H), 7.30 (d. 2H), 7.40 (d, 1H), 7.80 (d, 2H). 7.90 (s, 1H). **LRMS** (APCI): 563.8 (MH^+).

Example 51

3-1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl-6-cyano-1-methyl-1*H*-indole

(a) 6-cyano-1-methylindole



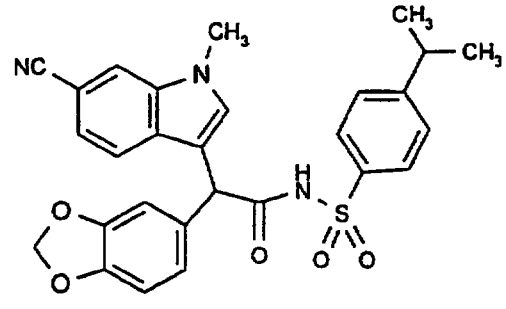
Cuprous cyanide (12.8g, 143mmol) was added to a stirred solution of 6-bromo-1-methylindole (10g. 47mmol) in N-methylpyrrolidinone (60ml) under a nitrogen atmosphere. The reaction mixture was heated at 150°C for 48h. The reaction mixture was cooled and partitioned between ethyl acetate (200ml) and aqueous ammonia (200ml of

0.88M). The organic layer was washed with brine (3 x 200ml), dried ($MgSO_4$) and concentrated. Flash column chromatography (elution with 70% hexane/30% ethyl acetate) gave the product as a crystalline white solid (5.3g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 3.80 (s, 3H), 6.60 (s, 1H), 7.25 (d, 1H), 7.35 (d, 1H), 7.70 (d, 2H).

LRMS (Thermospray): 174.1 (MNH_4^+).

(b) 3-[1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl]-6-cyano-1-methyl-1*H*-indole



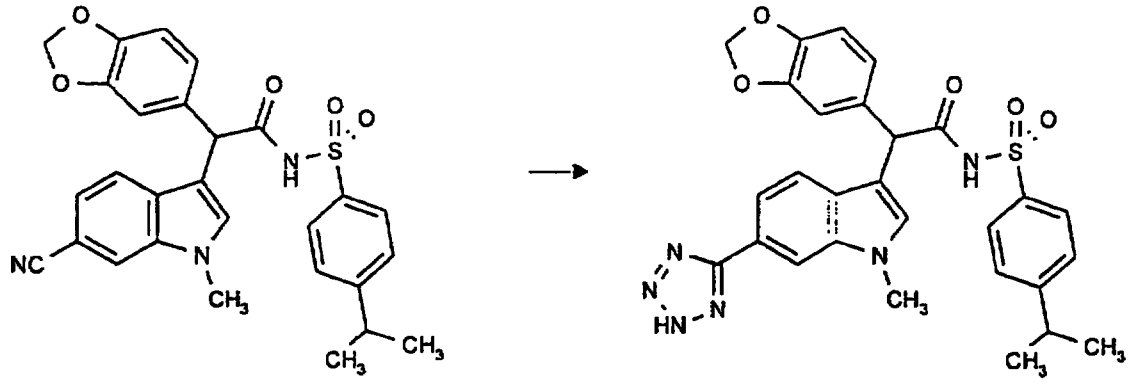
The title compound was prepared using the methods of Examples 1(d), 2 and 3, but starting with the compound of step (a) in place of 6-methoxycarbonyl-1-ethylindole.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.30 (d, 6H), 3.00 (m, 1H), 3.80 (s, 3H), 5.00 (s, 1H), 6.00 (s, 2H), 6.60 (s, 1H), 6.65 (d, 1H), 6.70 (d, 1H), 7.00 (s, 1H), 7.20 (s, 2H), 7.40 (d, 2H), 7.60 (s, 1H), 7.85 (d, 2H), 8.20 (s, 1H).

LRMS (APCI): 516.2 (MH^+).

Example 52

3-[1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl]-1-methyl-6-(2*H*-1,2,3,4-tetrazol-5-yl)-1*H*-indole



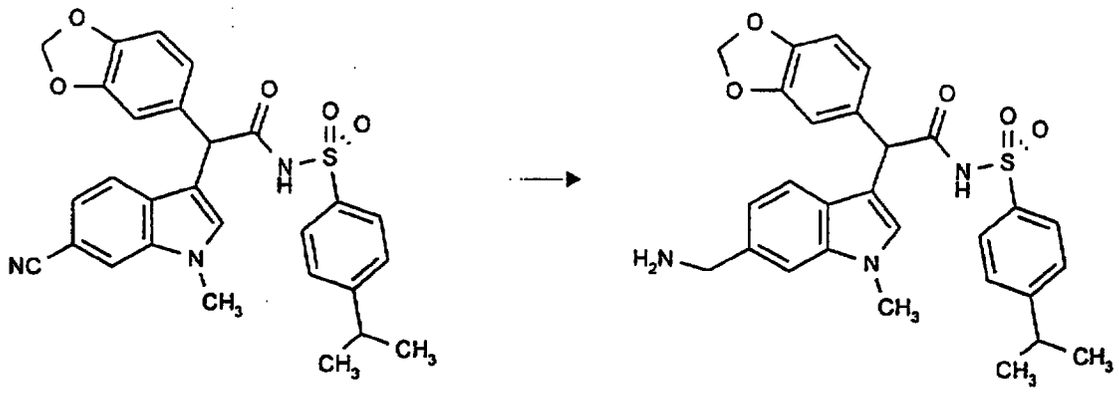
Trimethylsilylazide (0.23ml. 1.74mmol) and dibutyl tin oxide (52mg, 0.2mmol) were added to a solution of 3-{1-(1.3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-cyano-1-methyl-1*H*-indole (the product of Example 51. 300mg, 0.58mmol) in toluene (10ml) and the solution was heated at reflux under an atmosphere of nitrogen for 14h. Tlc analysis showed incomplete reaction. Further aliquots of trimethylsilylazide (0.23ml, 1.74mmol) and dibutyl tin oxide (52mg, 0.2mmol) were added and heating was continued at reflux for a further 24h. The reaction was cooled and concentrated. The crude product was purified by flash column chromatography (gradient elution from 95% dichloromethane /5% methanol to 90% dichloromethane /10% methanol) giving a pale pink solid (100mg).

^{1}H NMR (300MHz. d_6-DMSO): δ = 1.20 (d. 6H), 3.00 (m. 1H), 3.80 (s, 3H), 5.10 (s, 1H), 5.95 (s, 2H). 6.70 (d, 1H). 6.75 (s. 1H), 6.80 (d. 1H). 7.10 (s. 1H). 7.25 (d. 1H), 7.40 (d. 2H), 7.60 (d, 1H). 7.75 (d, 2H), 8.00 (s. 1H).

LRMS (APCI): 559 (MH^+).

Example 53

6-(Aminomethyl)-3-1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl-1-methyl-1*H*-indole



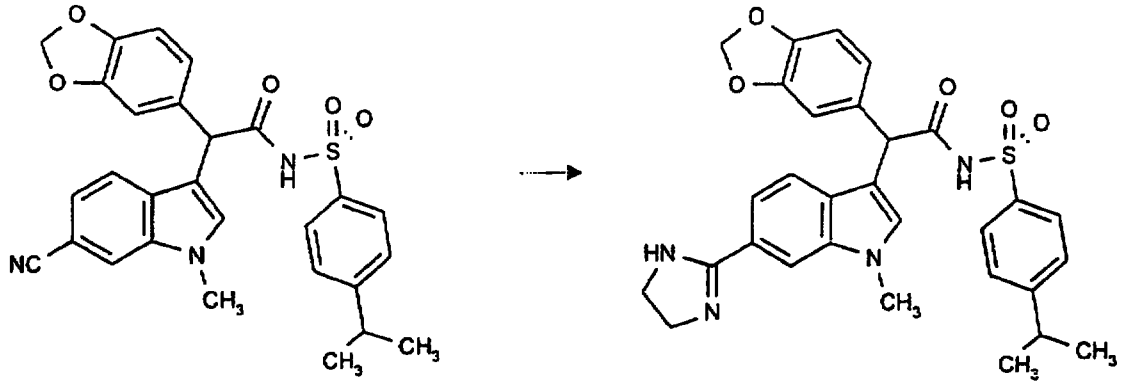
Sodium borohydride (213mg, 5.6mmol) was added slowly to a vigorously stirred solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-cyano-1-methyl-1*H*-indole (the product of Example 51, 290mg, 0.56mmol) and $CoCl_2.6H_2O$ (200mg, 0.84 mmol) in methanol (12ml) at room temperature under a nitrogen atmosphere. After 2h the reaction was complete and 2N hydrochloric acid (4ml) was added dropwise. Stirring was continued until the black precipitate had dissolved. The methanol was removed in vacuo and the product was extracted from water with dichloromethane(50ml) and ethyl acetate (50ml). The organic layers were combined, dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (elution with 90% dichloromethane /10% methanol /2% acetic acid) giving a brown gum. The residue was dissolved in methanol (10ml) and stirred with charcoal for 30 mins. Filtration and concentration gave the product as a yellow oil.

^{1}H NMR (300MHz, CD_3OD): δ = 1.20 (d, 6H), 2.95 (m, 1H), 3.65 (s, 3H), 4.20 (s, 2H), 5.00 (s, 1H), 5.80 (d, 2H), 6.60 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 7.00 (d, 1H), 7.25 (d, 3H), 7.40 (s, 1H), 7.80 (d, 2H).

LRMS (Thermospray): 520.4 (MH^+).

Example 54

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-(4,5-dihydro-1*H*-2-imidazolyl)-1-methyl-1*H*-indole



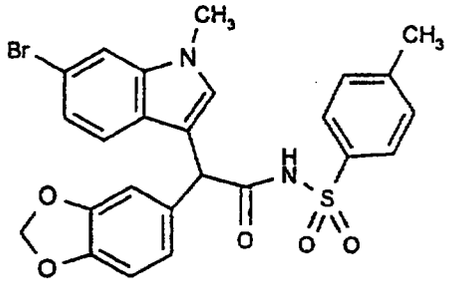
Diethyldithiophosphate (1.3ml. 7.7 mmol) was added to 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-cyano-1-methyl-1*H*-indole (the product of Example 51, 800mg, 1.5mmol) in a mixture of ethanol (10ml) and water (5 drops). The reaction was heated at reflux with stirring for 14h. After cooling the solvent was removed in vacuo and the residues purified by flash column chromatography (elution with 98% dichloromethane /2% methanol) to give a brown oil. This residue was dissolved in ethylenediamine and the reaction mixture heated at reflux for 3h. After cooling the ethylenediamine was removed in vacuo. Hydrochloric acid (10ml) was added and the resulting precipitate was filtered and washed with dichloromethane and methanol. Flash column chromatography (elution with 80% dichloromethane/20% methanol/5%NH_3) gave the product as a white solid.

^{1}H NMR (300MHz, d_6-DMSO): δ = 1.20 (d, 6H), 2.80 (m, 1H), 3.80 (s, 3H), 3.95 (s, 4H), 4.80 (s, 1H), 5.85 (s, 2H), 6.70 (d, 1H), 6.75 (d, 1H), 6.80 (s, 1H), 7.20 (d, 2H), 7.35 (s, 1H), 7.40 (d, 1H), 7.55 (d, 1H), 7.60 (d, 2H), 8.05 (s, 1H).

LRMS (Electrospray): 559.1 (MH^-).

Example 55

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole

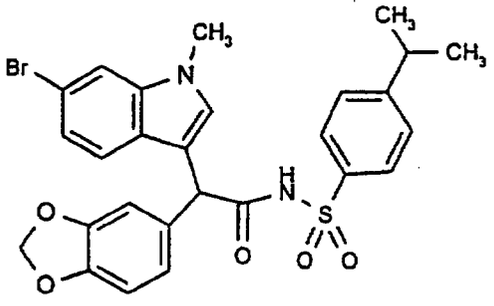


The title compound was prepared from the compound of Example 13(a), using the methods of Examples 1(d), 2 and 3, and using 4-methylbenzenesulphonamide in place of 4-iosopropylbenzenesulphonamide in the last step.

^{1}H NMR (300MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.70 (s, 3H), 4.90 (s, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.65 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H), 6.90 (d, 1H), 7.05 (d, 1H), 7.20 (d, 2H), 7.40 (s, 1H), 7.80 (d, 2H), 8.20 (brs, 1H).

Example 56

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole



The title compound was prepared from the compound of Example 13(a), using the methods of Examples 1(d), 2 and 3.

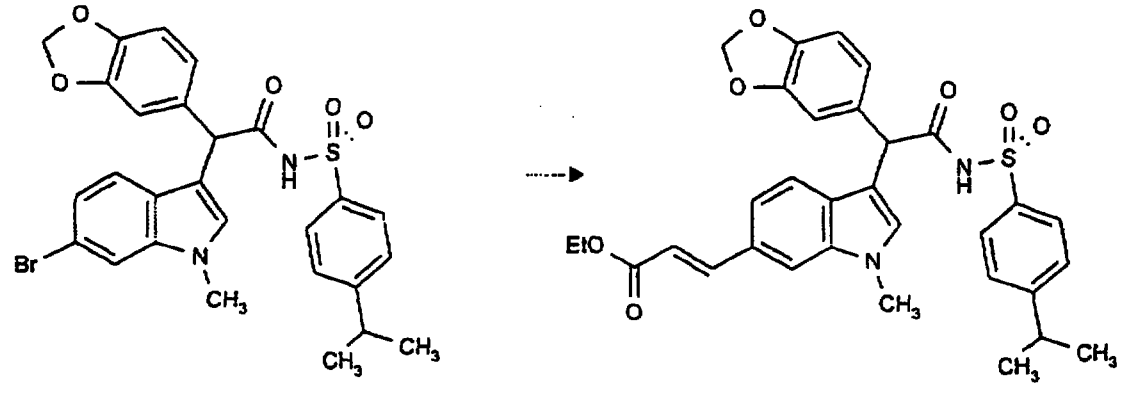
^{1}H NMR (300MHz, d_6-DMSO): δ = 1.20 (d, 6H), 3.00 (m, 1H), 3.60 (s, 3H), 5.00 (s, 1H), 5.90 (s, 2H), 6.70 (m, 3H), 6.85 (s, 1H), 6.95 (d, 1H), 7.00 (d, 1H), 7.40 (d, 2H), 7.60 (s, 1H), 7.75 (d, 2H).

LRMS (APCI): 568.9, 571.2 (MH^-).

Analysis: found C, 54.82; H, 4.39; N, 4.53; $C_{27}H_{25}N_2O_5SBr.H_2O$ requires C, 55.20; H, 4.63; N, 4.77.

Example 57

Ethyl (*E*)-3-[3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolyl]-2-propenoate



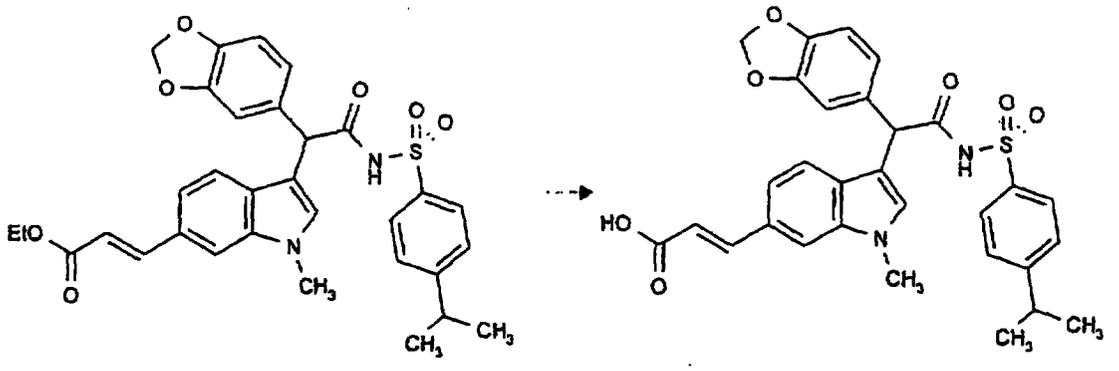
Palladium acetate (9.5mg, 0.042mmol) was added to a stirred solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole (the product of Example 56, 200mg, 0.35mmol), ethyl acrylate (0.048ml, 0.44mmol), triethylamine (0.146ml, 1mmol) and tri-o-tolylphosphine (32mg, 0.1mmol) in acetonitrile (10ml) at room temperature under a nitrogen atmosphere. The solution was heated at reflux for 2h. After cooling the mixture was poured into brine (50ml) and extracted with ethyl acetate (2 x 50ml). The organic layers were washed with water (50ml), dried ($MgSO_4$) and concentrated to give a grey foam. Purification by flash column chromatography (elution with 95% dichloromethane /5% methanol) gave the product as a pale yellow foam.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.30 (d, 6H), 1.35 (t, 3H), 3.00 (m, 1H), 3.75 (s, 3H), 4.30 (q, 2H), 5.00 (s, 1H), 5.95 (s, 2H), 6.40 (d, 1H), 6.70 (m, 3H), 6.90 (s, 1H), 7.10 (d, 1H), 7.20 (d, 1H), 7.35 (d, 2H), 7.40 (s, 1H), 7.80 (d, 1H), 7.85 (d, 2H), 8.20 (brs, 1H).

LRMS (Thermospray): 589.5 (MH^+).

Example 58

(*E*)-3-[3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolyl]-2-propenoic acid



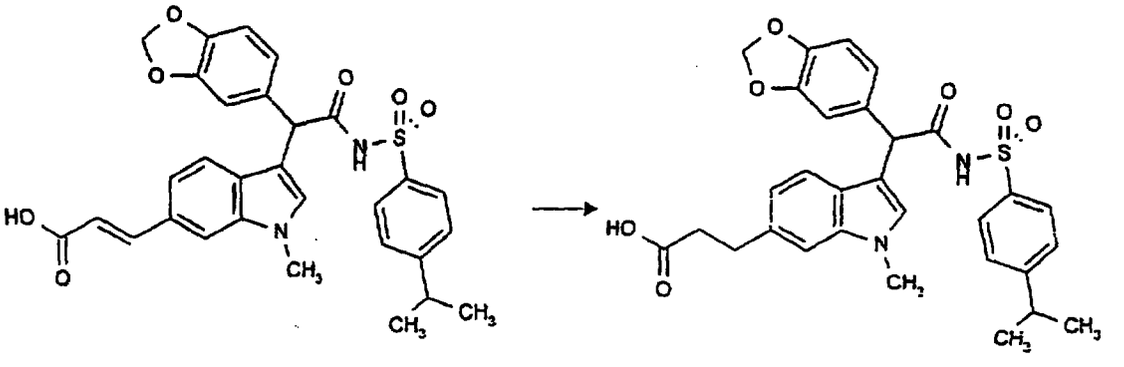
Ethyl (*E*)-3-(3-1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl-1-methyl-1*H*-6-indolyl)-2-propenoate (the product of Example 57, 120mg, 0.2mmol) was dissolved in a 1:1 mixture of tetrahydrofuran and methanol (5ml). Sodium hydroxide solution (0.6ml of 1N NaOH) was added and the mixture was heated to reflux with stirring. After 3h the solvent was removed in vacuo and the product was extracted from 1N hydrochloric acid (50ml) with ethyl acetate (2 x 50ml). The organic layers were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (gradient elution from 100% dichloromethane to 90% dichloromethane /10% methanol /1% acetic acid) gave the product as a pale green foam (90mg).

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.30 (d, 6H), 3.00 (m, 1H), 3.80 (s, 3H), 5.00 (s, 1H), 5.95 (s, 2H), 6.40 (d, 1H), 6.65 (m, 3H), 6.90 (s, 1H), 7.20 (m, 3H), 7.35 (d, 2H), 7.40 (s, 1H), 7.80 (d, 1H), 7.90 (d, 2H).

LRMS (Thermospray): 578.0 (MNH_4^+).

Example 59

3-[3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolyl]propanoic acid



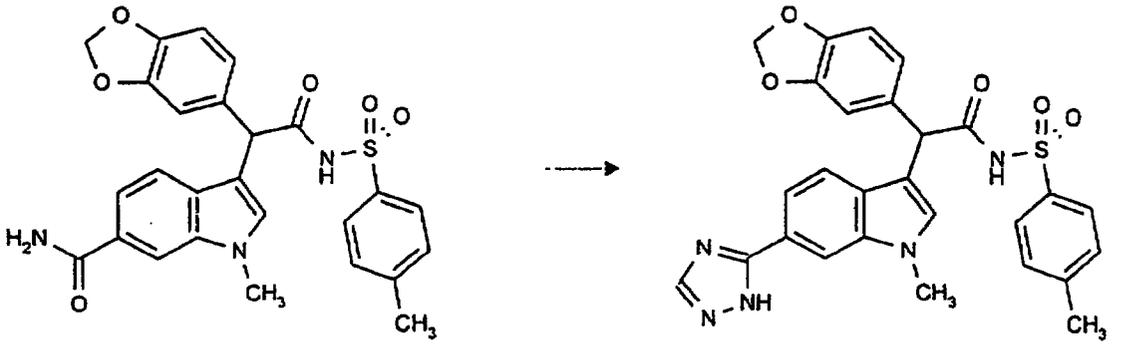
10% Palladium-on-carbon (10mg) was added to a stirred solution of (*E*)-3-[3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolyl]-2-propenoic acid (the compound of Example 58, 80mg, 0.14mmol) and ammonium formate (64mg, 0.5mmol) in a 1:1 mixture of tetrahydrofuran and ethanol (10ml total). The mixture was stirred at reflux for 48h, cooled, filtered through Arbocel™ and concentrated. The grey foam was purified by flash column chromatography (elution with 98% dichloromethane /2% methanol) giving the product as a white foam.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.25 (d, 6H), 2.70 (t, 2H), 3.00 (m, 3H), 3.60 (s, 3H), 4.95 (s, 1H), 5.90 (s, 2H), 6.60 (m, 4H), 6.80 (d, 1H), 7.00 (d, 1H), 7.10 (s, 1H), 7.40 (d, 2H), 7.80 (d, 2H), 8.20 (brs, 1H).

LRMS (Thermospray): 563.6 (MH^+).

Example 60

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-6-(4*H*-1,2,4-triazol-3-yl)-1*H*-indole



Dimethylformamide dimethylacetal (10ml) was added to 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-isopropylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-6-indolecarboxamide (the compound of Example 28, 180mg, 0.36 mmol) and the slurry was heated at reflux for 48h. The solvent was removed in vacuo and the residue redissolved in glacial acetic acid (8ml). Hydrazine hydrate (12mg, 4.68mmol) was added and the solution heated at reflux for 24h. After cooling the crude product was extracted from brine (50ml) with ethyl acetate (2 x 50ml). The organic layers were dried ($MgSO_4$) and concentrated. Flash column chromatography (elution with 96% dichloromethane /4% methanol) gave the desired product as a pale yellow solid.

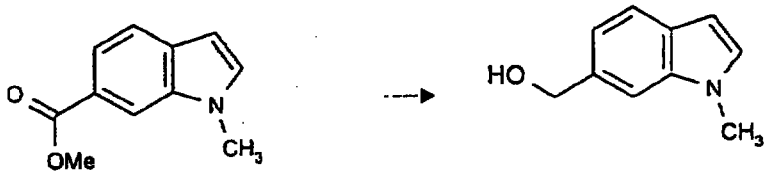
^{1}H NMR (300MHz, $CDCl_3$): δ = 2.40 (s, 3H), 2.55 (s, 3H), 5.00 (s, 1H), 5.80 (s, 2H), 5.90 (brs, 1H), 6.60 (s, 3H), 6.80 (s, 1H), 7.00 (d, 1H), 7.20 (d, 2H), 7.45 (d, 1H), 7.80 (d, 2H), 7.90 (s, 1H), 8.20 (s, 1H).

LRMS (APCI): 530.0 (MH^-).

Example 61

2-(1,3-Benzodioxol-5-yl)-2-[1-methyl-6-(triisopropylsilyloxymethyl)-1*H*-3-indolyl]acetic acid

(a) 6-Hydroxymethyl-1-methylindole

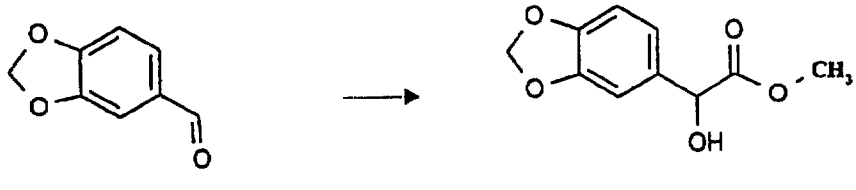


To a solution of 6-methoxycarbonyl-1-methylindole (prepared by the method of Example 1(b), but using 6-bromo-1-methylindole in place of 6-bromo-1-ethylindole, 5g) in tetrahydrofuran (30ml) at -70°C under a nitrogen atmosphere, was added diisobutyl aluminium hydride (66ml of a 1.0M solution in tetrahydrofuran) dropwise with stirring. The solution was stirred at -70°C for 15 mins then warmed to room temperature for 2 hours. The mixture was diluted with water (100ml) and partitioned between ethyl acetate and aqueous sodium hydroxide. The aqueous layer was re-extracted with ethyl acetate and combined organic extracts were dried ($MgSO_4$) and evaporated to give crude product which was purified by flash column chromatography using 80% ethyl acetate/20% hexane eluant to give the subtitle compound as a clear oil which solidified on standing (4.1g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.60 (s, 1H), 3.80 (s, 3H), 4.80 (d, 2H), 6.45 (s, 1H), 7.00 (s, 1H), 7.05 (d, 1H), 7.35 (s, 1H), 7.60 (d, 1H).

LRMS (Thermospray): 162.3 (MH^+)

(b) Methyl 2-(1,3-benzodioxol-5-yl)-2-hydroxyacetate



Lithium chloride (11.8g), potassium hydroxide (31.4g) and tetrabutylammonium bromide (4.5g) were dissolved in a mixture of 1,4-dioxane (120ml) and water (120ml). Piperonal (21g, 140mmol) was added to this vigorously stirred ice-cold mixture, and after 10 minutes bromoform (12.2ml 140mmol) was added dropwise over ~30 minutes. Stirring was

continued for 20 hours at ambient temperature. Water (500ml) was added and the mixture warmed to dissolve the precipitate. After washing with diethylether, the aqueous solution was acidified with concentrated hydrochloric acid. The crude carboxylic acid intermediate was isolated by extraction with diethylether and evaporation in vacuo. The residue was dissolved in methanol (500ml) and acidified with 20 drops of concentrated sulphuric acid. The solution was heated to reflux for 2 hours. then cooled and evaporated in vacuo. The residue was dissolved in diethylether and washed with water. The organic fraction was dried (magnesium sulphate), and concentrated in vacuo. Flash chromatography using dichloromethane as eluant, and then recrystallisation from diisopropylether gave 13.2g of the subtitle compound. (m.p. 93-95^{0}C)

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.35 (d, 1H exchangeable). 3.77 (s. 3H). 5.07 (d, 1H). 5.95 (s, 2H), 6.80 (d. 1H). 6.90 (s. 1H). 6.92 (d. 1H).

LRMS (Thermospray): 228.5 (MNH_4^+)

(c) Methyl 2-(1,3-benzodioxol-5-yl)-2-bromoacetate

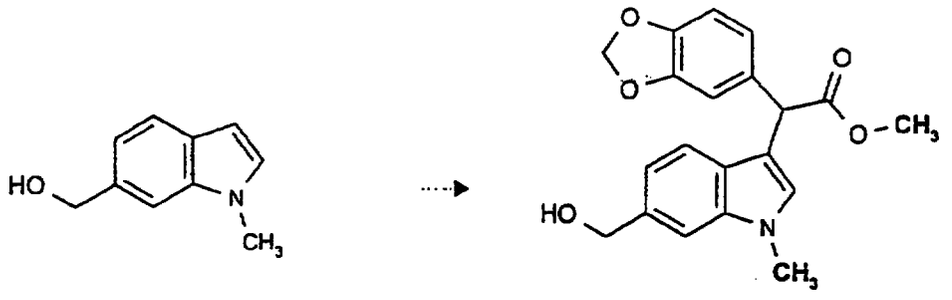


Hydrobromic acid (20ml of 62%w/v solution in water) was added to methyl 2-(1,3-benzodioxol-5-yl)-2-hydroxyacetate (from step (b). 11g. 52mmol) in toluene (200ml). After stirring for 3 hours the aqueous layer was removed and the organic layer was evaporated in vacuo. The residue was flash chromatographed, eluting with dichloromethane, and then crystallised with diisopropylether and hexane.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.76 (s, 3H). 5.26 (s. 1H). 5.95 (s. 2H). 6.70 (d. 1H). 6.92 (d, 1H), 7.09 (s, 1H).

m.p.: 39-41^{0}C

(d) Methyl 2-(1,3-benzodioxol-5-yl)-2-[6-(hydroxymethyl)-1-methyl-1*H*-3-indolyl]acetate

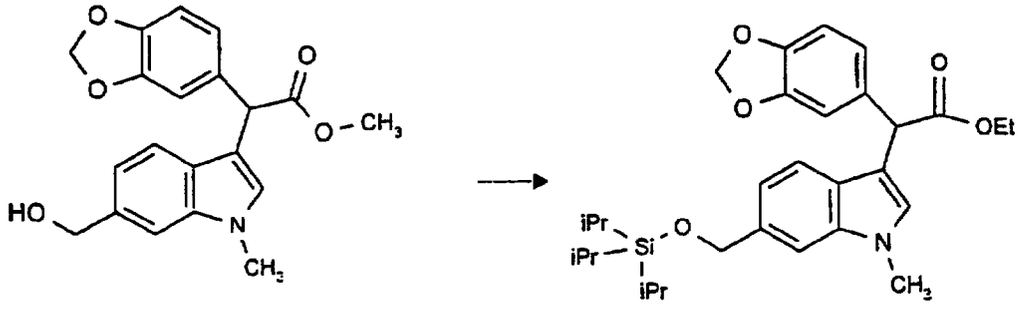


2,6-Dimethylpyridine (0.12ml) was added to a stirred solution of methyl 2-(1,3-benzodioxol-5-yl)-2-bromoacetate (from step (c), 273mg, 1mmol) and 6-(hydroxymethyl)-1-methylindole (from step (a), 161mg, 1mmol) in anhydrous dimethylformamide (2ml) at ambient temperature, under a nitrogen atmosphere. The solution was heated to 80°C for 3 hours. The reaction mixture was cooled, and partitioned between diethylether and water, separated and the organic layer dried (magnesium sulphate) and evaporated in vacuo. The residue was flash chromatographed (using diethyl ether as eluant) to give the subtitle compound as a colourless foam (273mg).

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.64 (t, 1H exchangeable), 3.72 (s, 3H), 3.76 (s, 3H), 4.79 (d, 2H), 5.16 (s, 1H), 5.90 (s, 2H), 6.73 (d, 1H), 6.85 (d, 1H), 6.90 (s, 1H), 7.03 (d, 1H), 7.08 (s, 1H), 7.31 (s, 1H), 7.40 (d, 1H).

LRMS (Thermospray): 353.9 (MH^+)

(e) <u>Methyl 2-(1,3-benzodioxol-5-yl)-2-[1-methyl-6-(triisopropylsilyloxymethyl)-1*H*-3-indolyl]acetate</u>



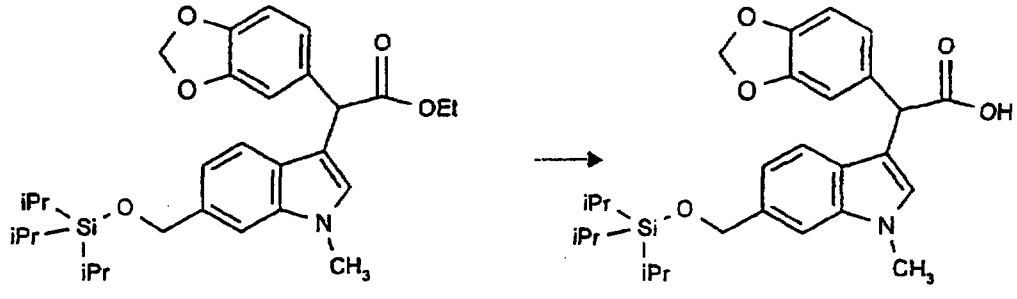
Chlorotriisopropylsilane (0.19ml, 0.88mmol) was added to a solution of methyl 2-(1,3-benzodioxol-5-yl)-2-[6-(hydroxymethyl)-1-methyl-1*H*-3-indolyl]acetate (from step (d), 260mg, 0.74mmol) and imidazole (100mg, 1.47mmol) in anhydrous dimethylformamide (3ml). After 3 hours the mixture was partitioned between diethyl ether and water, the

organic layer was separated and washed with water. The organic layer was dried (magnesium sulphate), and the solvent removed in vacuo. The residue was flash chromatographed (using 50% dichloromethane, 50% hexane as eluent) to give the subtitle compound (305mg) as an oil.

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.00-1.20 (m, 21H), 3.74 (s, 3H), 3.75 (s, 3H), 4.95 (s, 2H), 5.15 (s, 1H), 5.90 (d, 2H), 6.72 (d, 1H), 6.88 (d, 1H), 6.91 (s, 1H), 7.00 (d, 1H), 7.03 (s, 1H), 7.34 (s, 1H), 7.36 (d, 1H).

LRMS (Thermospray): 510.4 (MH^+).

(f) 2-(1,3-Benzodioxol-5-yl)-2-[1-methyl-6-(triisopropylsilyloxymethyl)-1*H*-3-indolyl]acetic acid

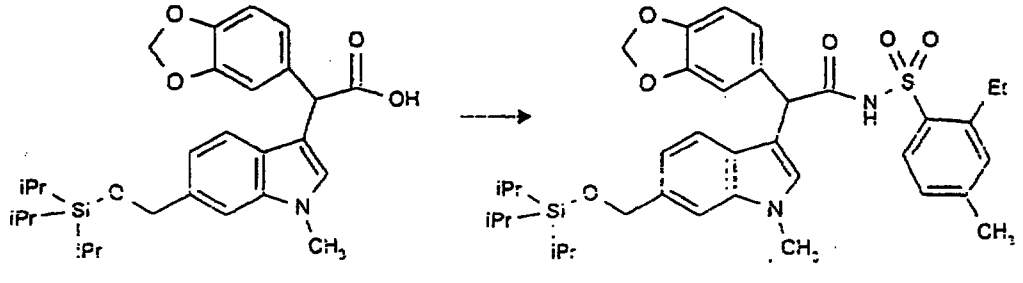


The subtitle compound was prepared by the method of Example 2 from the compound of step (e).

^{1}H NMR (300MHz, $CDCl_3$): δ = 1.03-1.22 (m, 21H), 3.72 (s, 3H), 4.96 (s, 2H), 5.18 (s, 1H), 5.91 (s, 2H), 6.72 (d, 1H), 6.88 (d, 1H), 6.90 (s, 1H), 7.00 (d, 1H), 7.06 (s, 1H), 7.36 (s, 1H), 7.37 (d, 1H).

LRMS (Thermospray): 497.1 (MH^+)

(g) 3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-ethyl-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(triisopropylsilyloxymethyl)-1-methyl-1*H*-indole

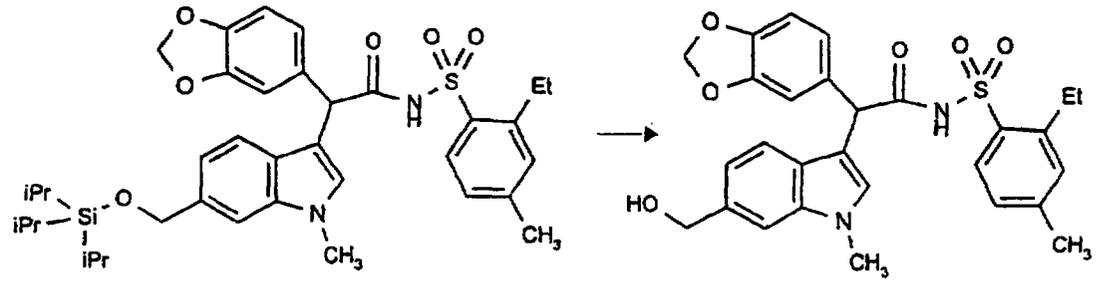


1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (113mg. 0.59mmol) was added to a stirred solution of 2-(1.3-benzodioxol-5-yl)-2-[6-(triisopropylsilyloxymethyl)-1-methyl-1*H*-3-indolyl]acetic acid (from step (f). 250mg. 0.49mmol), N,N-dimethylaminopyridine (78mg. 0.64mmol) and the sulphonamide from Preparation 1 (107mg. 0.54mmol) in dichloromethane (6ml) at room temperature under a nitrogen atmosphere. After 12h the reaction mixture was poured into 1N hydrochloric acid (50ml) and extracted with dichloromethane (2 x 50ml). The organic fractions were dried ($MgSO_4$) and concentrated to give a yellow foam. Flash column chromatography (elution with 98% dichloromethane /2% methanol) gave the subtitle (95mg) as a white foam.

^{1}H NMR (400MHz. $CDCl_3$): δ = 1.00 (t. 3H). 1.10 (d. 18H). 1.15 (m. 3H). 2.35 (s. 3H). 2.50 (q. 2H). 3.60 (s. 3H). 4.90 (s. 2H). 4.95 (s. 1H). 5.80 (s. 2H). 6.65 (m. 3H). 6.70 (s. 1H). 6.90 (d. 1H). 7.05 (s. 1H). 7.10 (m. 2H). 7.35 (s. 1H). 8.00 (d. 1H).

LRMS (Thermospray): 677.4 (MH^+).

(h) 3-{1-(1.3-Benzodioxol-5-yl)-2-[(2-ethyl-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(hydroxymethyl)-1-methyl-1*H*-indole

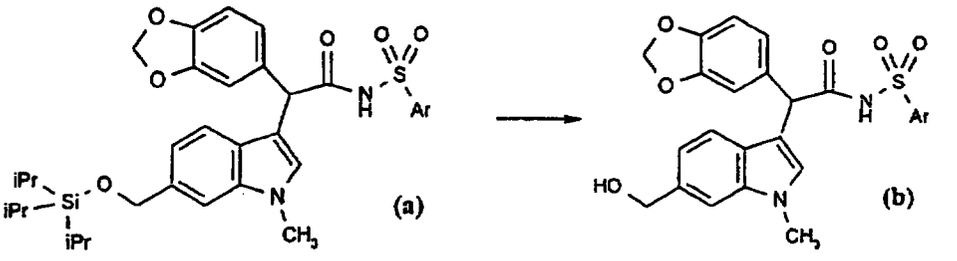


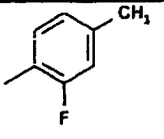
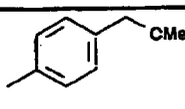
Tetraethylammonium fluoride (312mg, 2.18mmol) was added to a stirred solution of the compound of step (g) (380mg, 0.55 mmol) in acetonitrile (6ml) at room temperature under a nitrogen atmosphere. After 12h the mixture was poured into 1M hydrochloric acid (50ml) and extracted into ethyl acetate (2 x 50ml). The organic fractions were combined. dried ($MgSO_4$) and concentrated in vacuo to give a yellow foam. Flash column chromatography (eluting with 98% dichloromethane /2% methanol) gave the product as a white solid (242mg).

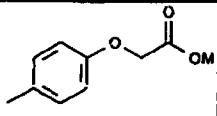
^{1}H NMR (400MHz. $CDCl_3$): δ = 1.15 (t. 2H). 2.30 (s. 3H). 2.60 (q. 2H). 3.60 (s. 3H). 4.75 (s. 2H). 5.25 (s. 1H). 5.80 (s. 2H). 6.60 (m. 3H). 6.80 (s. 1H). 6.95 (d. 1H). 7.05 (s. 1H). 7.10 (d. 2H). 7.20 (s. 1H). 8.00 (d. 1H).

LRMS (Thermospray): 538.2 (MNH_4^+).

Examples 62-64 were prepared by the methods of Example 61, but using the appropriate sulphonamide in the penultimate step.



Example N°	Ar	Physical Data
62(a)*		**^{1}H NMR** (300MHz, $CDCl_3$): δ = 1.05 (d, 18H), 1.20 (m, 3H), 2.40 (s, 3H), 3.75 (s, 3H), 4.95 (s, 3H), 5.95 (s, 2H), 6.70 (d, 2H), 6.75 (s, 1H), 6.80 (s, 1H), 6.90 (d, 1H), 7.00 (d, 1H), 7.10 (d, 1H), 7.20 (d, 1H), 7.40 (s, 1H), 7.90 (t, 1H), 8.25 (s, 1H). **LRMS** (APCI): 668.0 (MH^+).
62(b)	"	**^{1}H NMR** (400MHz, d_6-DMSO): δ = 2.30 (s, 3H), 3.60 (s, 3H), 4.50 (s, 2H), 5.00 (brs, 1H), 5.10 (s, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.65 (d, 1H), 6.80 (d, 1H), 6.85 (s, 1H), 6.90 (d, 1H), 7.10 (d, 1H), 7.15 (d, 1H), 7.20 (d, 1H), 7.25 (s, 1H), 7.50 (s, 1H), 7.70 (t, 1H), 12.50 (s, 1H). **LRMS** (Thermospray): 511.2 (MH^+).
63(a)		**^{1}H NMR** (400MHz, $CDCl_3$): δ = 1.10 (d, 18H), 1.15 (m, 3H), 3.40 (s, 3H), 3.65 (s, 3H), 4.45 (s, 2H), 4.90 (s, 3H), 5.90 (s, 2H), 6.60 (m, 3H), 6.90 (d, 1H), 7.00 (d, 1H), 7.30 (s, 1H), 7.40 (d, 2H), 7.85 (d, 2H), 8.05 (s, 1H). **LRMS** (APCI): 681.6 (MH^+).
63(b)	"	**^{1}H NMR** (400MHz, d_6-DMSO): δ = 3.25 (s, 3H), 3.60

		(s, 3H), 4.45 (s, 2H), 4.50 (m, 2H), 5.00 (brs, 1H), 5.05 (s, 1H), 5.80 (s, 2H), 6.60 (s, 1H), 6.65 (d, 1H), 6.75 (d, 2H), 6.85 (d, 1H), 7.00 (d, 1H), 7.25 (s, 1H), 7.40 (d, 2H), 7.80 (d, 2H), 12.4 (brs, 1H). **LRMS** (Thermospray): 523.4 (MH^+).
64(a)		^{1}**H NMR** (400MHz, $CDCl_3$): δ = 1.05 (d, 18H), 1.20 (m, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 4.60 (s, 2H), 4.90 (s, 3H), 5.85 (s, 2H), 6.60 (m, 4H), 6.90 (d, 3H), 7.00 (d, 1H), 7.35 (s, 1H), 7.80 (d, 2H), 8.10 (brs, 1H). **LRMS** (APCI): 723.0 (MH^+).
64(b)	"	^{1}**H NMR** (400MHz, $CDCl_3$): δ = 2.00 (brs, 1H), 3.60 (s, 3H), 3.75 (s, 3H), 4.60 (s, 2H), 4.70 (s, 2H), 5.00 (s, 1H), 5.80 (s, 2H), 6.60 (d, 1H), 6.70 (d, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 6.85 (d, 2H), 6.90 (d, 1H), 7.10 (d, 1H), 7.20 (s, 1H), 7.80 (d, 2H). **LRMS** (APCI): 567 (MH^+).

* See Preparation 2 for sulphonamide preparation

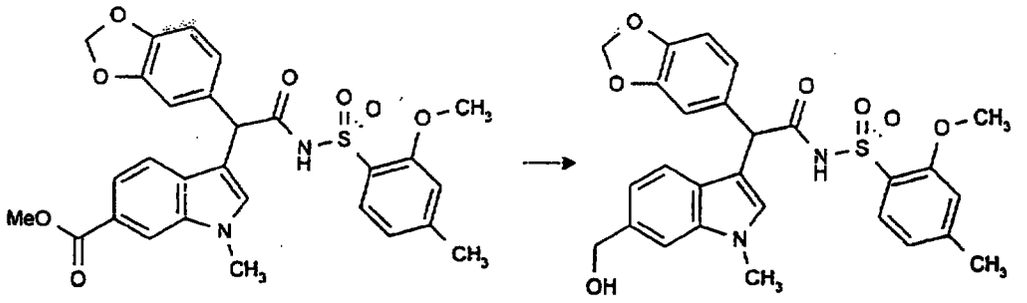
Example 65

3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(hydroxymethyl)-1-methyl-1*H*-indole

(a) 3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(methoxycarbonyl)-1-methyl-1*H*-indole

The subtitle compound was prepared using the methods of Examples 1(b), 1(d), 2 and 3, but starting with 6-bromo-1-methylindole in place of 6-bromo-1-ethylindole, and reacting with the sulphonamide of Preparation 11 in the method of Example 3.

(b) 3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(hydroxymethyl)-1-methyl-1*H*-indole



Lithium aluminium hydride (15mg, 0.2 mmol) was added slowly to a stirred solution of methyl 3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxo-ethyl}-1-methyl-1*H*-6-indolecarboxylate (from step (a), 220mg, 0.4mmol) in tetrahydrofuran at 0°C under a nitrogen atmosphere. After 2h a further 1 equivalent (30mg) of lithium aluminium hydride was added and the mixture was warmed to room temperature. After 1h ethyl acetate (10ml) was carefully added and the product extracted from 1N hydrochloric acid with ethyl acetate (2 x 50ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (elution with 95% dichloromethane /5% methanol) gave the product as a white solid (130mg).

^{1}H NMR (400MHz, CD_3OD): δ = 2.45 (s, 3H), 3.55 (s, 3H), 3.75 (s, 3H), 4.75 (s, 2H), 5.15 (s, 1H), 5.95 (d, 2H), 6.70 (s, 1H), 6.75 (m, 3H), 6.85 (s, 1H), 6.95 (d, 1H), 7.00 (d, 1H), 7.25 (d, 1H), 7.35 (s, 1H), 7.85 (d, 1H).

LRMS (Thermospray): 523.7 (MH^+).

Analysis:	Found: C, 61.00; H, 5.12; N, 5.19.
$C_{27}H_{26}N_2O_7S.0.5H_20$;	Requires: C, 61.00; H, 5.12; N, 5.27.

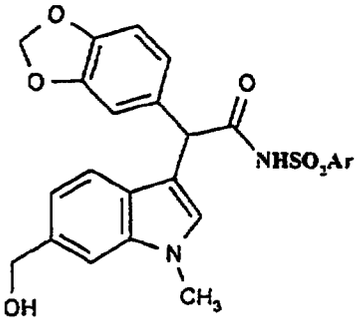
m.p. = 184-186°C

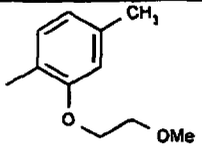
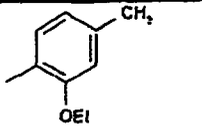
The title compound was separated into its individual enantiomers using a Chiralpak™ AD column (25 x 2 cm) with a flow rate of 10ml/min using a 70:30 mix of hexane:iso-propylalcohol with 0.6% trifluoroacetic acid and 0.4% diethylamine added. The products were detected at 220nm and had retention times of 32min and 39min.

The enantiomeric purity was checked by chromatographing 100μl of the eluent from the above separation, using a Chiralpak™ AD column (25 x 0.46cm), a flow rate of 1ml/min and a 70:30 mix of hexane:iso-propylalcohol with 0.3% trifluoroacetic acid and 0.2%

diethylamine added as eluant. The products were detected at 220nm and had retention times of 15.5min and 18min.

Examples 66 and 67 were prepared by the method of Example 65, but using the sulphonamides of Preparations 10 and 9 respectively.

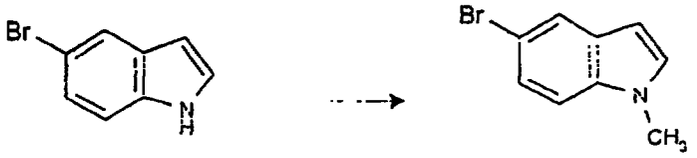


Example N°	Ar	Physical Data
66		**^{1}H NMR** (300MHz $CDCl_3$): 2.40 (s, 3H), 3.25 (s, 3H), 3.40 - 4.00 (m, 2H), 3.70 (s, 3H), 4.80 (d, 2H), 5.05 (s, 1H), 5.90 (s, 2H), 5.60 - 7.40 (m, 9H), 7.90 (d, 2H), 9.00 (s, 1H). **LRMS** (Thermospray): 567.1 (MH^-)
67		**^{1}H NMR** (400MHz d_6-DMSO): 1.10 (t, 3H), 2.30 (d, 2H), 3.60 (s, 3H), 3.70 - 3.90 (m, 2H), 4.50 (d, 2H), 5.00 (t, 1H), 5.15 (s, 1H), 5.90 (d, 2H), 6.60 - 7.65 (m, 10H), 12.05 (s, 0.5H), 12.30 (s, 0.5H). **LRMS** (Thermospray): 537.4 (MH^-)

Example 68

2-(1,3-Benzodioxol-5-yl)-2-(5-bromo-1-methyl-1*H*-3-indolyl)acetic acid

(a) 5-Bromo-1-methylindole

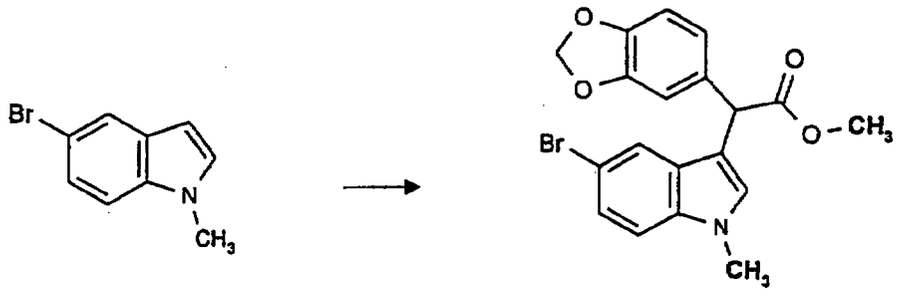


Sodium hydride (440mg of a 60% dispersion in paraffin wax) was added to a stirred solution of 5-bromoindole (1.96g. 10mmol) in dimethylformamide (20ml) at ambient temperature under a nitrogen atmosphere. After 30 minutes methyl p-toluenesulphonate (2.05g 11mmol) was added. After 20 hours the mixture was partitioned between diethyl ether and water. The organic layer was separated and washed twice with water. The organic layer was dried (magnesium sulphate) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (using 50% hexane. 50% dichloromethane as eluant) to give 2.07g of product as a waxy solid.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.75 (s, 3H). 6.42 (d. 1H). 7.05 (d, 1H). 7.17 (d, 1H), 7.28 (d, 1H), 7.75 (s, 1H).

LRMS (Thermospray): 212 (MH^+)

(b) Methyl 2-(1,3-benzodioxol-5-yl)-2-(5-bromo-1-methyl-1*H*-3-indolyl)acetate

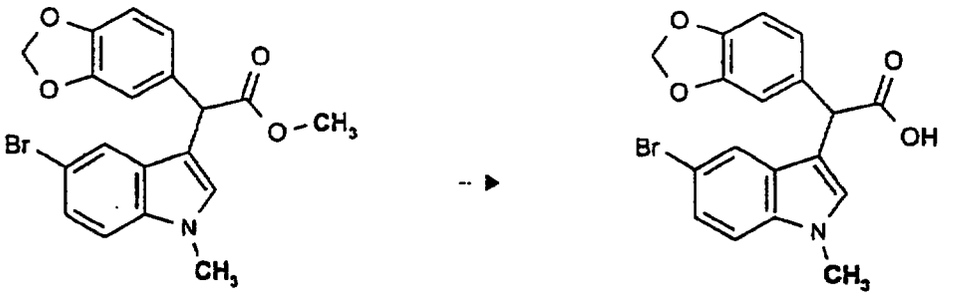


2.6-Dimethylpyridine (0.75ml) was added to a stirred solution of methyl 2-(1,3-benzodioxol-5-yl)-2-bromoacetate (from Example 61(c), 1.75g, 6.43mmol) and 5-bromo-1-methylindole (from step (a), 1.35g) in anhydrous dimethylformamide (10ml) at ambient temperature. under a nitrogen atmosphere. The solution was heated to 80°C for 8 hours. The reaction mixture was partitioned between diethylether and water. separated and the organic layer dried (magnesium sulphate) and evaporated in vacuo. The residue was flash chromatographed (using 50% dichloromethane and 50% hexane as eluant) to give the subtitle compound as a colourless oil (1.98g).

^{1}H NMR (300MHz. $CDCl_3$): δ = 3.72 (s. 3H). 3.74 (s. 3H). 5.09 (s. 1H). 5.92 (s. 2H). 6.75 (d. 1H). 6.85 (d. 1H). 6.88 (s, 1H). 7.10 (s. 1H). 7.15 (d. 1H). 7.28 (d. 1H). 7.55 (s. 1H).

LRMS (Thermospray): 402.0. 404.0 (MH^+).

(c) 2-(1,3-Benzodioxol-5-yl)-2-(5-bromo-1-methyl-1*H*-3-indolyl)acetic acid



Aqueous sodium hydroxide (14.7ml of 1M) was added to a solution of methyl 2-(1,3-benzodioxol-5-yl)-2-(5-bromo-1-methyl-1*H*-3-indolyl)acetate from (b) (1.97g, 4.9mmol) in a 3:1 mixture of methanol and 1,4-dioxane at ambient temperature. The mixture was heated to reflux for 1 hour before recooling and removing the organic solvents in vacuo. The residue was redissolved in water and acidified with drops of concentrated hydrochloric acid. The resultant precipitate was extracted with diethylether, dried (magnesium sulphate) and the solvent removed in vacuo. The residue was crystallised from diisopropylether to give the subtitle compound (1.59g).

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.74 (s, 3H), 5.09 (s, 1H), 5.92 (s, 2H), 6.75 (d, 1H), 6.85 (d, 1H), 6.88 (s, 1H), 7.10 (s, 1H), 7.15 (d, 1H), 7.28 (d, 1H), 7.55 (s, 1H).

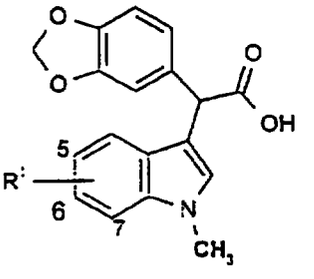
LRMS (Thermospray): 388.4, 390.4 (MH^+)

Analysis: Found C, 55.61; H, 3.66; N, 3.51.

$C_{18}H_{14}BrNO_4$ requires: C, 55.69; H, 3.64; N, 3.60.

m.p.: 191-193^{0}C

Examples 69-78 were prepared by the method of Example 68, starting with the appropriately substituted indole.



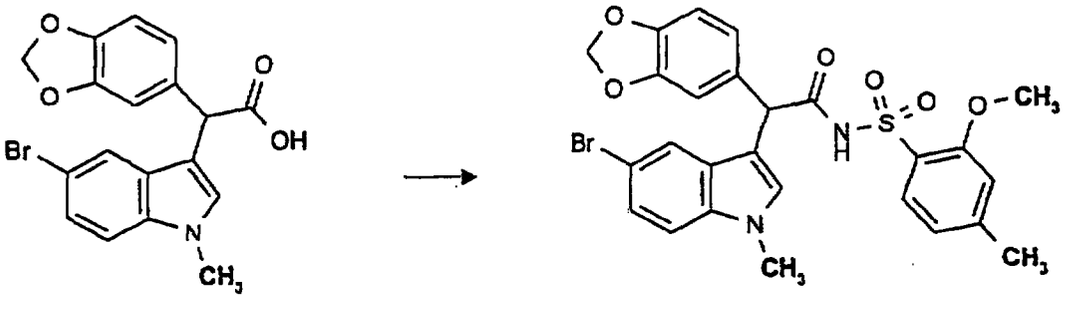
Example	R' =	Data

69	5-F ($C_{18}H_{14}FNO_4$)	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 3.75 (s, 3H), 5.10 (s, 1H), 5.92 (s, 2H), 6.74 (d, 1H), 6.83-7.00 (m, 3H), 7.06 (d, 1H), 7.15 (s, 1H), 7.18 (m, 1H) **LRMS** (Thermospray): 328.2 (MH^+)
70	5-NC ($C_{19}H_{14}N_2O_4$)	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 3.80 (s, 3H), 5.15 (s, 1H), 5.94 (s, 2H), 6.76 (d, 1H), 6.84 (s, 1H), 6.85 (d, 1H), 7.26 (s, 1H), 7.32 (d, 1H), 7.42 (d, 1H), 7.75 (s, 1H). **LRMS** (Thermospray): 352.3 (MH^+)
71	5-CH_3O ($C_{19}H_{17}NO_5$)	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 3.72 (s, 3H), 3.78 (s, 3H), 5.13 (s, 1H), 5.92 (s, 2H), 6.77 (d, 1H), 6.86 (m, 2H), 6.92 (s, 1H), 7.06 (s, 1H), 7.16-7.27 (m, 2H). **LRMS** (Thermospray): 340.4 (MH^+)
72	6-F ($C_{18}H_{14}FNO_4$)	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 3.70 (s, 3H), 5.13 (s, 1H), 5.92 (s, 2H), 6.70-6.98 (m, 5H), 7.06 (s, 1H), 7.33 (m, 1H). **LRMS** (Thermospray): 327.8 (MH^+) **m.p.:** 150-152^{0}C
73	6-Cl ($C_{18}H_{14}ClNO_4$)	**^{1}H NMR** (300MHz, d_6-DMSO): δ = 3.75 (s, 3H), 5.08 (s, 1H), 5.95 (s, 2H), 6.80-6.90 (m, 3H), 6.97 (d, 1H), 7.27 (s, 1H), 7.40 (d, 1H), 7.50 (s, 1H), 12.50 (br, 1H exchangeable). **LRMS** (Thermospray): 343.9 (MH^+)
74	6-Br ($C_{18}H_{14}BrNO_4$)	**^{1}H NMR** (400MHz, d_6-DMSO): δ = 3.71 (s, 3H), 5.03 (s, 1H), 5.90 (d, 2H), 6.75-6.82 (m, 2H), 6.84 (s, 1H), 7.06 (d, 1H), 7.22 (s, 1H), 7.32 (d, 1H), 7.61 (s, 1H), 12.60 (br, 1H exchangeable). **Analysis:** Found: C, 55.50; H, 3.60; N, 3.54. $C_{18}H_{14}BrNO_4$ Requires: C, 55.69; H, 3.64; N, 3.60.
75	7-F ($C_{18}H_{14}FNO_4$)	**^{1}H NMR** (400MHz, $CDCl_3$): δ = 3.93 (s, 3H), 5.10 (s, 1H), 5.90 (s, 2H), 6.72 (d, 1H), 6.80-6.93 (m, 4H), 7.02 (s, 1H), 7.11 (d, 1H).

		LRMS (Thermospray): 328.2 (MH^+)
76	7-Cl ($C_{18}H_{14}ClNO_4$)	**^{1}H NMR** (400MHz, $CDCl_3$): δ = 4.09 (s, 3H), 5.10 (s, 1H), 5.90 (s, 2H), 6.72 (d, 1H), 6.82 (d,1H), 6.83 (s, 1H), 6.88 (t, 1H), 7.01 (s, 1H), 7.10 (s, 1H), 7.28 (d, 1H). **LRMS** (Thermospray): 344.2 (MH^+) **m.p.:** 146-147°C
77	7-Br ($C_{18}H_{14}BrNO_4$)	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 4.10 (s, 3H), 5.10 (s, 1H), 5.90 (s, 2H), 6.71 (d, 1H), 6.80-6.86 (m, 3H), 7.03 (s, 1H), 7.29-7.34 (m, 2H). **LRMS** (Thermospray): 388.1 (MH^+) **m.p.:** 151°C
78	6-CN ($C_{19}H_{14}N_2O_4$)	**^{1}H NMR** (400MHz, $CDCl_3$): δ = 3.80 (s, 3H), 5.15 (s, 1H), 5.80 (s, 2H), 6.75 (d, 1H), 6.85 (m, 1H), 7.25 (m, 2H), 7.40 (d, 1H), 7.60 (s, 1H). **LRMS** (Thermospray): (MH^+).

Example 79

3-[1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl]-5-bromo-1-methyl-1*H*-indole



4-Dimethylaminopyridine (151mg) was added to a solution of 2-(1,3-benzodioxol-5-yl)-2-(5-bromo-1-methyl-1*H*-3-indolyl)acetic acid (the product of Example 68, 480mg, 1.24mmol) in anhydrous dichloromethane (10ml) at ambient temperature. 2-Methoxy-4-methyl-1-benzenesulfonamide (from Preparation 11, 300mg, 1.48mmol) was added to the solution, followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (355mg, 1.85mmol), and stirring was continued for 20 hours. The solution was washed twice with 2N hydrochloric acid, and dried (magnesium sulphate) and the solvents

removed in vacuo. The residue was flash chromatographed using 1% methanol in dichloromethane as eluant. and crystallised from dichloromethane and diethyl ether mixture to give the subtitle compound (535mg).

^{1}H NMR (400MHz. d_6-DMSO): δ = 2.30 (s. 3H). 3.55 (s. 3H). 3.64 (s. 3H). 5.10 (s. 1H). 5.90 (d, 2H). 6.63 (d. 1H). 6.66 (s. 1H). 6.72-7.00 (m. 4H). 7.19 (d. 1H). 7.32 (d. 1H). 7.34 (s, 1H), 7.62 (d, 1H), 11.70 (s, 1H exchangeable).

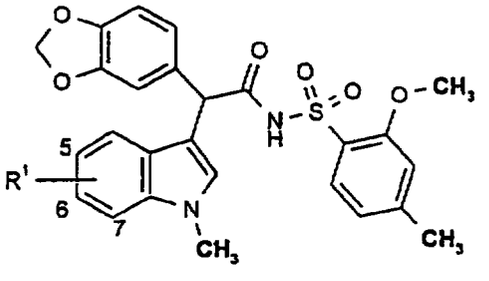
LRMS (Thermospray): 588.2 (MNH_4^+)

Analysis: Found C, 53.79; H, 4.29; N, 4.62.

$C_{26}H_{23}BrN_2O_6S$; 0.5 H_2O requires: C, 53.80; H, 4.17; N, 4.83.

m.p.: 145-150^{0}C.

Examples 80-88 were prepared by the method of Example 79 using the carboxylic acids of Examples 69-76 and 78 respectively.



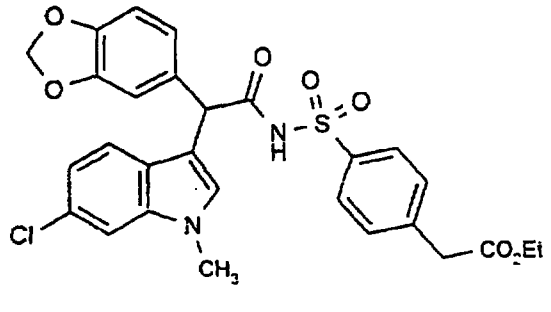
Example	R' =	Data
80	5-F ($C_{26}H_{23}FN_2O_6S$)	**^{1}H NMR** (400MHz, $CDCl_3$): δ = 2.37 (s. 3H). 3.45 (s, 3H), 3.68 (s, 3H). 4.96 (s, 1H). 5.88 (s. 2H), 6.60 (s, 1H). 6.63-6.69 (m. 3H). 6.74-6.96 (m. 4H). 7.15 (m. 1H). 7.89 (d, 1H), 8.50 (br. 1H exchangeable). **LRMS** (Thermospray): 511.4 (MH^+). 528.1 (MNH_4^+)
81	5-NC	**^{1}H NMR** (300MHz. $CDCl_3$): δ = 2.42 (s. 3H). 3.63 (s. 3H). 3.75 (s. 3H). 5.03 (s. 1H). 5.94 (s. 2H), 6.68 (s. 1H). 6.70-6.76 (m. 3H). 6.90 (d. 1H). 7.02 (s. 1H). 7.30 (d. 1H). 7.42 (d. 1H). 7.50 (s. 1H). 7.90 (d. 1H).

		8.38 (brs. 1H exchangeable). **LRMS** (Thermospray): 535.0 (MNH_4^+) **Analysis**: Found: C. 61.54; H. 4.75: N. 7.49. $C_{27}H_{23}N_3O_6S$: 0.5 H_2O Requires: C. 61.59; H. 4.59; N. 7.98.
82	5-CH_3O	**^{1}H NMR** (300MHz, $CDCl_3$): δ = 2.40 (s. 3H), 3.35 (s. 3H). 3.62 (s, 3H). 3.74 (s, 3H), 5.00 (s, 1H), 5.92 (s. 2H). 6.58 (m, 2H). 6.70-6.78 (m, 3H), 6.80 (s. 1H), 6.82-6.90 (m, 2H). 7.20 (d. 1H), 7.92 (d. 1H), 8.40 (brs, 1H exchangeable). **LRMS** (Thermospray): 523.0 (MH^+)
83	6-F ($C_{26}H_{23}FN_2O_6S$)	**^{1}H NMR** (400MHz. $CDCl_3$): δ = 2.37 (s, 3H). 3.41 (s. 3H). 3.60 (s, 3H). 4.96 (s, 1H), 5.88 (s, 2H), 6.55 (s, 1H). 6.62-6.70 (m, 4H), 6.81 (s, 1H), 6.80-6.90 (m, 2H). 7.08 (m, 1H). 7.89 (d, 1H), 8.80 (br. 1H exchangeable). **LRMS** (Thermospray): 511.4 (MH^+)
84	6-Cl ($C_{26}H_{23}ClN_2O_6S$)	**^{1}H NMR** (300MHz, d_6-DMSO): δ = 2.35 (s, 3H), 3.62 (s. 3H). 3.70 (s, 3H), 5.18 (s. 1H), 5.92 (s, 2H). 6.68-6.74 (m, 2H), 6.80 (d. 1H), 6.87 (d, 1H). 6.93-7.00 (m. 3H). 7.20 (d. 1H). 7.50 (s, 1H), 7.67 (d. 1H), 12.25 (s, 1H exchangeable). **LRMS** (Thermospray): 526.9 (MH^+)
85	6-Br ($C_{26}H_{23}BrN_2O_6S$)	**^{1}H NMR** (400MHz. $CDCl_3$): δ = 2.38 (s. 3H), 3.40 (s. 3H). 3.60 (s. 3H). 4.95 (s, 1H), 5.88 (s. 2H). 6.55 (s. 1H). 6.64 (m, 3H). 6.82 (m, 2H), 7.00 (m. 2H). 7.36 (s. 1H). 7.87 (d. 1H). 8.75 (br. 1H exchangeable). **LRMS** (APCI): 571.8 (MH^+) **Analysis**: Found: C. 52.20: H. 3.91: N. 4.62. $C_{26}H_{23}BrN_2O_6S$: 0.4 CH_2Cl_2 requires: C. 52.38: H. 3.96: N. 4.63. **m.p.**: 145-150°C (dec.).

86	7-F ($C_{26}H_{23}FN_2O_6S$)	**^{1}H NMR** (400MHz. $CDCl_3$): δ = 2.38 (s. 3H). 3.47 (s, 3H). 3.84 (s. 3H). 4.98 (s. 1H). 5.90 (s. 2H). 6.59 (s, 1H). 6.67 (s. 3H). 6.77 (s. 1H). 6.80-6.96 (m. 3H). 6.93 (m. 1H). 7.88 (d. 1H). 8.50 (br. 1H exchangeable). **LRMS** (Thermospray): 511.2 (MH^+). 528.1 (MNH_4^+). **m.p.:** 123-124^{0}C
87	7-Cl ($C_{26}H_{23}ClN_2O_6S$)	**^{1}H NMR** (300MHz. $CDCl_3$): δ = 2.38 (s. 3H). 3.47 (s, 3H). 3.89 (s. 3H). 4.98 (s. 1H). 5.90 (s, 2H). 6.59 (s, 1H). 6.66 (s. 3H). 6.75 (s. 1H). 6.80-6.90 (m, 2H), 7.03-7.13 (m. 2H). 7.85 (d. 1H). 8.40 (br, 1H exchangeable). **LRMS** (APCI): 528.7 (MH^-) **m.p.:** 233-234^{0}C
88	6-CN ($C_{27}H_{23}N_3O_6S$)	**^{1}H NMR** (400MHz. $CDCl_3$): δ = 2.40 (s, 3H). 3.50 (s, 3H). 3.70 (s. 3H). 5.00 (s. 1H). 5.90 (s, 2H). 6.60 (d, 1H). 6.65 (d. 1H). 6.65 (s. 1H). 6.80 (d. 1H). 7.10 (s, 1H). 7.15 (d. 1H). 7.20 (s. 1H). 7.25 (d. 1H). 7.55 (s, 1H). 7.85 (d. 1H). 8.70 (s. 1H). **LRMS** (APCI): 517.8 (MH^-).

Example 89

Ethyl 2-(4-[2-(1,3-benzodioxol-5-yl)-2-(6-chloro-1-methyl-1*H*-3-indolyl)acetyl]-sulfamoylphenyl)acetate



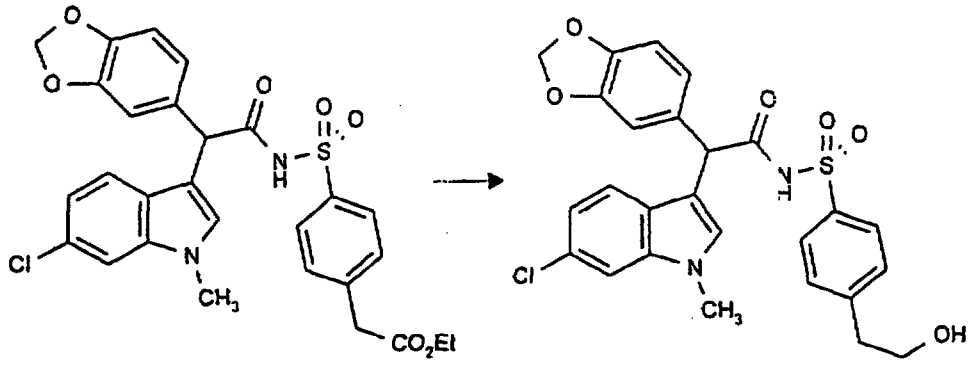
The title compound was prepared by the method of Example 79 from the compound of Example 73 and the appropriate sulphonamide.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.15 (t, 3H), 3.60 (s, 3H), 3.80 (s, 2H), 4.00 (q, 2H), 5.00 (s, 1H), 5.85 (s, 2H), 6.60 (m, 2H), 6.75 (d, 1H), 6.85 (s 1H), 6.90 (d, 1H), 7.05 (d, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 7.80 (d, 2H).

LRMS (Thermospray): 585.9, 588.6 (MNH_4^+).

Example 90

3-[1-(1,3-Benzodioxol-5-yl)-2-[4-(2-hydroxyethyl)phenyl]sulfonamido-2-oxoethyl]-6-chloro-1-methyl-1*H*-indole



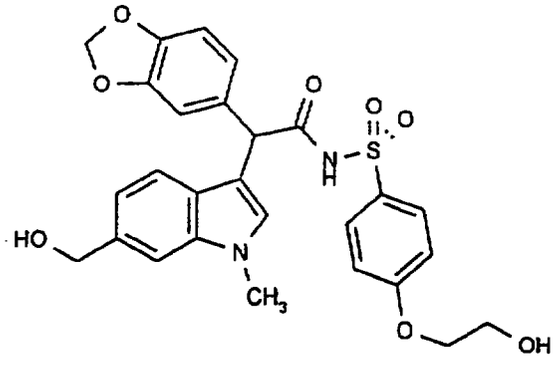
Lithium aluminium hydride (6mg, 0.16mmol) was added to a stirred solution of ethyl 2-(4-[2-(1,3-benzodioxol-5-yl)-2-(6-chloro-1-methyl-1*H*-3-indolyl)acetyl]sulfamoylphenyl)acetate (the product of Example 89, 80mg, 0.14mmol) in tetrahydrofuran (6ml) at 0°C under a nitrogen atmosphere. After 40mins ethyl acetate (1ml) was slowly added and the reaction mixture was poured into hydrochloric acid (50ml). The product was extracted into ethyl acetate (2 x 50ml), dried ($MgSO_4$) and concentrated. Recrystallisation (methanol/ether) gave the product as a white crystalline solid (50mg).

^{1}H NMR (400MHz, d_6-DMSO): δ = 2.80 (t, 2H), 3.60 (t, 2H), 3.65 (s, 3H), 4.60 (brs, 1H), 5.00 (s, 1H), 5.95 (s, 2H), 6.65 (d, 1H), 6.70 (s, 1H), 6.80 (d, 1H), 6.90 (s, 1H), 6.95 (d, 1H), 7.10 (d, 1H), 7.40 (d, 2H), 7.45 (s, 1H), 7.75 (d, 2H).

LRMS (Thermospray): 544.0, 545.7 (MNH_4^+).

Example 91

3-(1-(1,3-Benzodioxol-5-yl)-2-[4-(2-hydroxyethoxy)phenyl]sulfonamido-2-oxoethyl)-6-hydroxymethyl-1-methyl-1*H*-indole



The title compound was prepared by the method of Example 90 from the compound of Example 64(b).

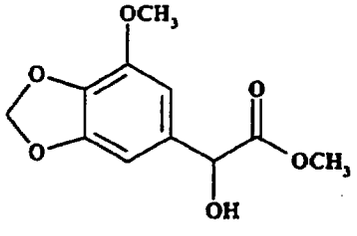
^{1}H NMR (400MHz, $CDCl_3$): δ = 3.50 (s. 3H), 3.60 (t, 1H), 3.80 (m, 2H). 3.90 (t, 1H), 3.95 (m. 2H), 4.55 (d. 2H), 4.95 (s. 1H), 5.70 (s, 2H). 6.50 (d. 1H), 5.95 (s. 1H), 6.60 (d, 1H), 6.65 (d, 1H), 6.80 (d. 3H). 6.90 (d, 1H). 7.10 (s. 1H). 7.70 (d. 2H).

LRMS (APCI): 540.0 (MH^+).

Example 92

6-Bromo-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)-sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole

(a) Methyl 2-hydroxy-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate

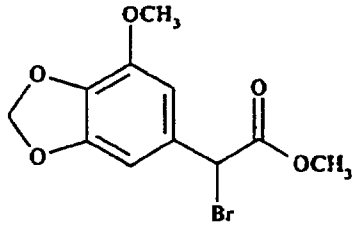


The subtitle compound was prepared using the method of Example 61(b) from 7-methoxy-1,3-benzodioxole-5-carbaldehyde (12.6g) as a waxy solid (4.5g).

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.40 (d. 1H exchangeable). 3.76 (s. 3H). 3.90 (s. 3H), 5.06 (d, 1H), 5.97 (s, 2H). 6.59 (s, 1H). 6.61 (s. 1H).

LRMS (Thermospray): 258 (MNH_4^+)

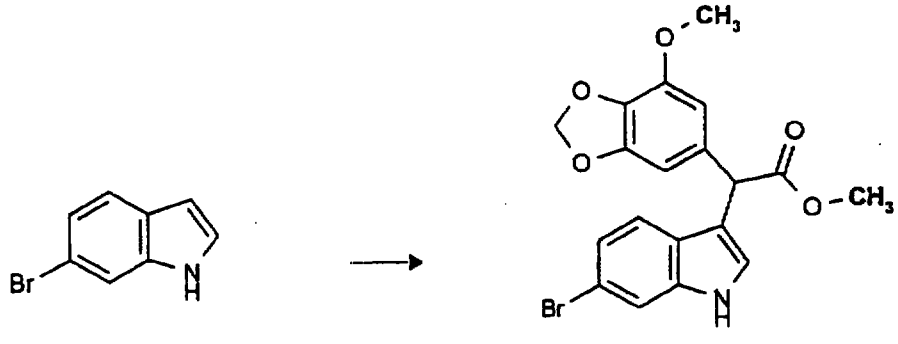
(b) Methyl 2-bromo-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate



The subtitle compound was prepared from methyl 2-hydroxy-2-(7-methoxy-1.3-benzodioxol-5-yl)acetate (the product of step (a). 4.45g. 19mmol) by the method of Example 61(c) (yield 2.25g).

^{1}H NMR (300MHz. $CDCl_3$): δ = 3.80 (s. 3H). 3.92 (s. 3H), 5.25 (s. 1H). 5.98 (s. 2H), 6.73 (s, 1H), 6.78 (s, 1H).

(c) Methyl 2-(6-bromo-1*H*-3-indolyl)-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate

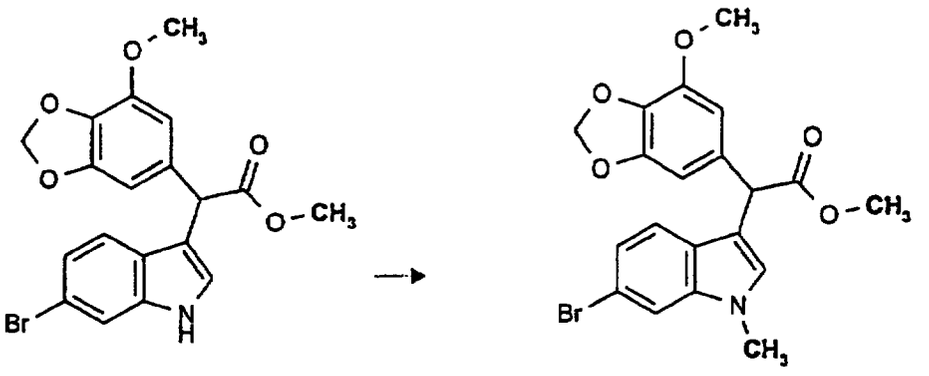


Methyl magnesium bromide (3.6ml of 3M solution in diethyl ether) was added dropwise to a stirred solution of 6-bromo-indole (2.13g. 10.9mmol) in toluene (20ml) under a nitrogen atmosphere. After 20 minutes the reaction mixture was transferred via a cannula. over ~10 minutes, to a stirred solution of methyl 2-bromo-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate (from step (b). 2.2g. 7.26mmol) in toluene (20ml) at ambient temperature. After a further 2 hours the mixture was poured into a mixture of diethyl ether and aqueous ammonium chloride. The organic layer was separated and dried (magnesium sulphate). and the solvent was removed in vacuo. The residue was flash chromatographed using dichloromethane as eluant to give the subtitle compound (2.7g).

^{1}H NMR (300MHz. $CDCl_3$): δ = 3.72 (s. 3H), 3.83 (s. 3H). 5.08 (s. 1H). 5.92 (s. 2H). 6.58 (s. 2H), 7.10-7.30 (m. 3H). 7.50 (s. 1H). 8.1 (br. 1H).

LRMS (Thermospray): 420.1 (MH^+)

(d) Methyl 2-(6-bromo-1-methyl-1*H*-3-indolyl)-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate

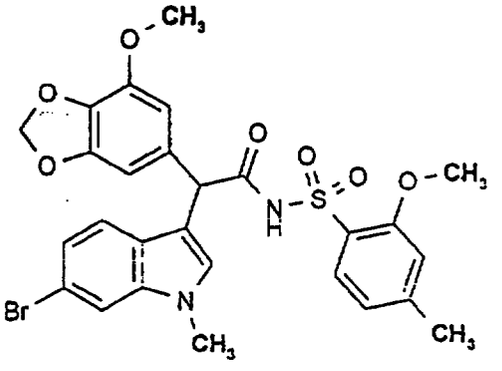


Sodium hydride (289mg of a 60% dispersion in paraffin wax) was added in portions to a stirred solution of methyl 2-(6-bromo-1*H*-3-indolyl)-2-(7-methoxy-1,3-benzodioxol-5-yl)acetate (from step (c). 2.7g, 6.5mmol) in anhydrous dimethylformamide (20ml) at 0°C under a nitrogen atmosphere. After 30 minutes, methyl p-toluenesulphonate (1.34g, 7.2mmol) was added. After a further 1 hour the mixture was partitioned between diethyl ether and water. The organic layer was separated and washed twice with water. The organic layer was dried (magnesium sulphate) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (using 30% hexane, 70% dichloromethane as eluant) to give 1.49g of the subtitle compound.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.72 (s, 3H), 3.75 (s, 3H), 3.85 (s, 3H), 5.08 (s, 1H), 5.92 (s, 2H), 3.78 (s, 2H), 7.04 (s, 1H), 7.17 (d, 1H), 7.28 (s, 1H), 7.43 (s, 1H).

LRMS (Thermospray): 432.2 (MH^+)

(e) 6-Bromo-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)-sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



The title compound was prepared from the product of step (d) using the methods of Examples 68(c) and 79.

^{1}H NMR (300MHz, d_6-DMSO): δ = 2.36 (s, 3H), 3.60 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 5.12 (s, 1H), 5.95 (s, 2H), 6.39 (s, 1H), 6.45 (s, 1H), 6.88 (d, 1H), 6.95 (s, 2H), 7.07 (d, 1H), 7.17 (d, 1H), 7.62 (s, 1H), 7.64 (d, 1H), 12.20 (s, 1H exchangeable).

LRMS (APCI): 602.9 (MH^+)

Analysis: Found: C, 53.47; H, 4.11; N, 4.62.

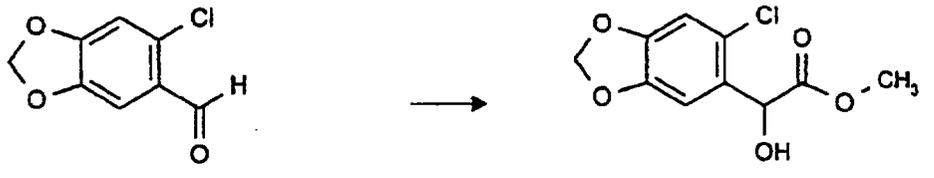
$C_{27}H_{25}BrN_2O_7S$; requires: C, 53.91; H, 4.19; N, 4.66.

m.p.: 235°C (dec.) from methanol.

Example 93

6-Bromo-3-{1-(6-chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole

(a) Methyl 2-(6-chloro-1,3-benzodioxol-5-yl)-2-hydroxyacetate



The subtitle compound was prepared by the method of Example 61(b), but starting with 6-chloro-1,3-benzodioxole-5-carbaldehyde (12.9g). Yield 9.4g. m.p.: 66-68°C.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.42 (d, 1H exchangeable), 3.77 (s, 3H), 5.48 (d, 1H), 5.98 (s, 2H), 6.82 (s, 1H), 6.83 (s, 1H).

LRMS (Thermospray): 262 (MNH_4^+)

(b) Methyl 2-bromo-2-(6-chloro-1,3-benzodioxol-5-yl)acetate



Thionyl bromide (3.7ml) was added to a stirred solution of methyl 2-(6-chloro-1,3-benzodioxol-5-yl)-2-hydroxyacetate from step (a) (7.8g, 32mmol) in toluene (50ml) at ambient temperature. After 6 hours the reaction mixture was evaporated in vacuo, and the

residue was flash chromatographed using dichloromethane as eluant, followed by crystallisation from diisopropylether to give the subtitle compound (7.6g).

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.80 (s, 3H), 5.87 (s, 1H), 6.00 (d, 2H), 6.80 (s, 1H), 7.26 (s, 1H).

(c) Methyl 2-(6-bromo-1*H*-3-indolyl)-2-(6-chloro-1,3-benzodioxol-5-yl)acetate

The subtitle compound was prepared following the procedure of Example 92(c), using methyl 2-bromo-2-(6-chloro-1,3-benzodioxol-5-yl)acetate from step (b). m.p. 172-174^{0}C. from diethyl ether and hexane.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.72 (s, 3H), 5.58 (s, 1H), 5.86 (d, 2H), 6.70 (s, 1H), 6.83 (s, 1H), 7.10-7.30 (m, 3H), 7.50 (s, 1H), 8.10 (br, 1H).

LRMS (Thermospray): 441.2 (MH^+)

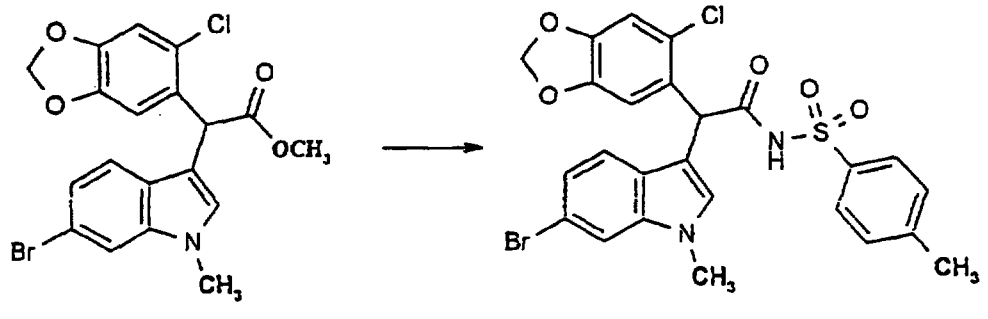
(d) Methyl 2-(6-bromo-1-methyl-1*H*-3-indolyl)-2-(6-chloro-1,3-benzodioxol-5-yl)acetate

The subtitle compound was prepared following the procedure of Example 92(d), using methyl 2-(6-bromo-1*H*-3-indolyl)-2-(6-chloro-1,3-benzodioxol-5-yl)acetate from step (c). m.p. 183-185^{0}C, from diisopropyl ether.

^{1}H NMR (300MHz, $CDCl_3$): δ = 3.75 (s, 3H), 3.76 (s, 3H), 5.60 (s, 1H), 5.90 (d, 2H), 6.77 (s, 1H), 6.87 (s, 1H), 7.06 (s, 1H), 7.17 (d, 1H), 7.30 (d, 1H), 7.45 (s, 1H).

LRMS (Thermospray): 437.9 (MH^+)

(e) 6-Bromo-3-{1-(6-chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



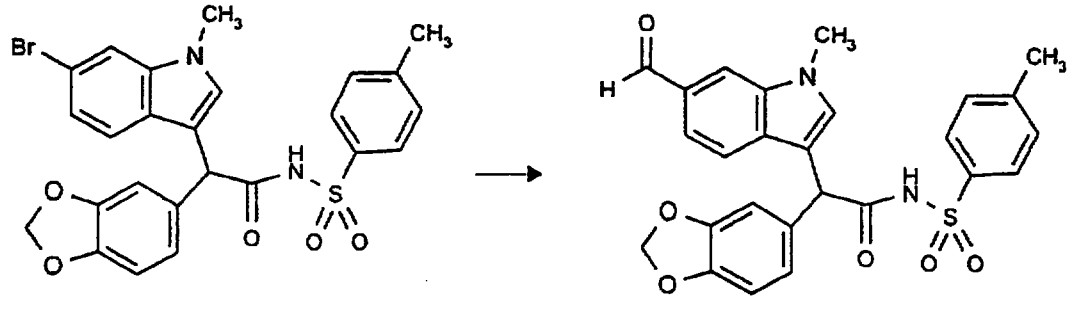
The subtitle compound was prepared from the compound of step (d) following the methods of Examples 68(c) and 79, and using the appropriate sulphonamide in the last step.

^{1}H NMR (300MHz. $CDCl_3$): δ = 2.46 (s. 3H). 3.71 (s. 3H). 5.36 (s. 1H). 5.90 (s. 2H). 6.48 (s. 1H). 6.82 (s. 1H). 6.85 (s. 1H). 7.00 (d. 1H). 7.07 (d. 1H). 7.28 (d. 2H). 7.45 (s. 1H). 7.83 (d, 2H). 8.25 (s. 1H exchangeable).

LRMS (APCI): 575.0 (MH^-)

Example 94

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-formyl-1-methyl-1*H*-indole



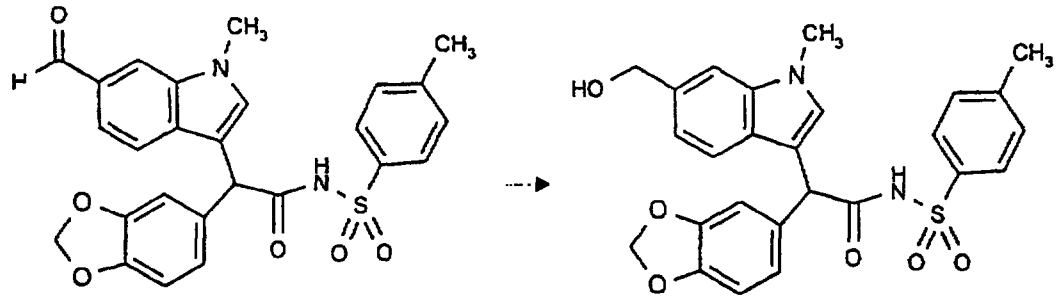
Carbon monoxide was bubbled through a stirred solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole (from Example 55. 400mg, 0.79 mmol), sodium formate (107mg, 1.57 mmol) and dichloro-bis(triphenylphosphine)-palladium (II) (11mg, 0.016mmol) in dimethylformamide (6ml) at 110°C for 4h. The reaction mixture was cooled and extracted from 1N hydrochloric acid with ethyl acetate (2 x 50ml). The organic layers were dried ($MgSO_4$) and concentrated. Flash column chromatography (elution with 95% dichloromethane /5% methanol) gave the product (320mg) as a fawn solid.

^{1}H NMR (400MHz. $CDCl_3$): δ = 2.40 (s, 3H), 3.80 (s. 3H). 5.05 (s. 1H). 5.90 (s, 2H). 6.60 (m, 3H), 7.05 (s, 1H). 7.2-7.6 (m. 4H), 7.80 (m, 3H). 9.20 (brs, 1H). 10.00 (s. 1H).

LRMS (Thermospray): 491.4 (MH^-).

Example 95

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(hydroxymethyl)-1-methyl-1*H*-indole



Sodium borohydride (51mg, 1.33mmol) was added to a stirred solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole (from Example 94, 305mg, 0.66mmol) in ethanol (10ml) at room temperature under a nitrogen atmosphere. After 1h the ethanol was removed in vacuo and the product was extracted from 0.5N hydrochloric acid (50ml) with dichloromethane (2 x 50ml). The organic layers were dried ($MgSO_4$) and concentrated. Flash column chromatography (elution with 95% dichloromethane /5% methanol) gave the product (230mg) as a white foam.

^{1}H NMR (400MHz, d_6-DMSO): δ = 2.35 (s, 3H), 3.60 (s, 3H), 4.50 (s, 2H), 4.95 (brs, 1H), 5.05 (s, 1H), 5.90 (s, 2H), 6.60 (s, 1H), 6.65 (d, 1H), 6.70 (d, 2H), 6.80 (d, 1H), 7.00 (d, 1H), 7.20 (s, 1H), 7.35 (d, 2H), 7.70 (d, 2H).

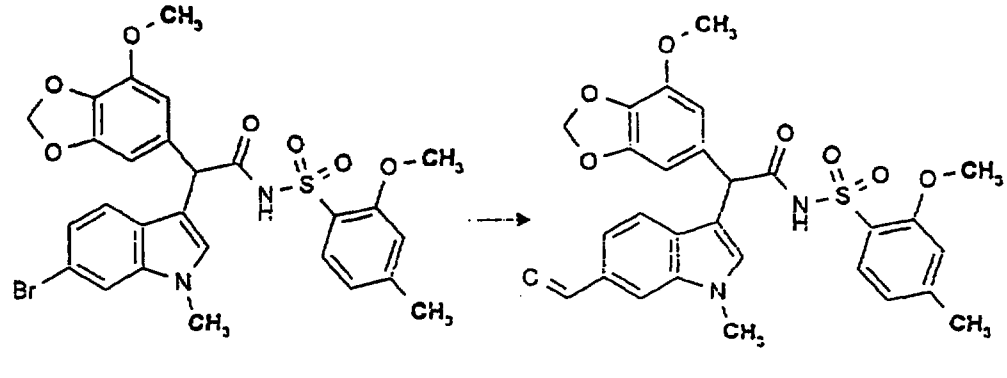
LRMS (Thermospray): 493.2 (MH^+).

Analysis: Found: C, 60.40; H, 5.29; N, 5.79.

$C_{26}H_{23}BrN_2O_6S.1.5H_2O$; requires: C, 60.10; H, 5.24; N, 5.39.

Example 96

6-Formyl-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)-sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



n-Butyllithium (0.8ml of 2.5M solution in hexane) was added to a stirred solution of 6-bromo-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)-sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole (from Example 92, 400mg, 0.67mmol) in anhydrous tetrahydrofuran at -75^{0}C under a nitrogen atmosphere. After 30 minutes dimethylformamide (0.15ml) was added to the orange solution, and after a further 30 minutes the mixture was allowed to warm to 0^{0}C before quenching with excess 1N hydrochloric acid. Ethyl acetate was added and the organic layer was separated and washed with water. The organic layer was dried (magnesium sulphate), and the solvents removed in vacuo. The residue was flash chromatographed using 1% methanol in dichloromethane as eluant, and the product was crystallised from dichloromethane and diethyl ether mixture to give the title compound (187mg).

^{1}H NMR (300MHz, d_6-DMSO): δ = 2.33 (s, 3H), 3.61 (s, 3H), 3.72 (s, 3H), 3.80 (s, 3H), 5.20 (s, 1H), 5.94 (s, 2H), 6.42 (s, 1H), 6.50 (s, 1H), 6.87 (d, 1H), 6.95 (s, 1H), 7.28 (s, 1H), 7.40 (d, 1H), 7.50 (d, 1H), 7.66 (d, 1H), 8.02 (s, 1H), 10.00 (s, 1H), 12.28 (brs, 1H exchangeable).

LRMS (APCI): 550.3 (MH^+)

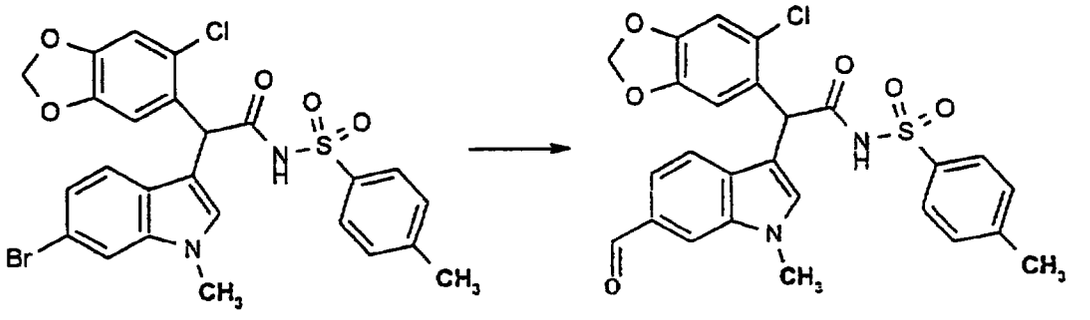
Analysis: Found: C, 61.24; H, 5.17; N, 4.61.

$C_{28}H_{26}N_2O_8S$: requires: C, 61.08; H, 4.76; N, 5.09.

m.p.: 233^{0}C- dec.

Example 97

3-{1-(6-Chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-formyl-1-methyl-1*H*-indole



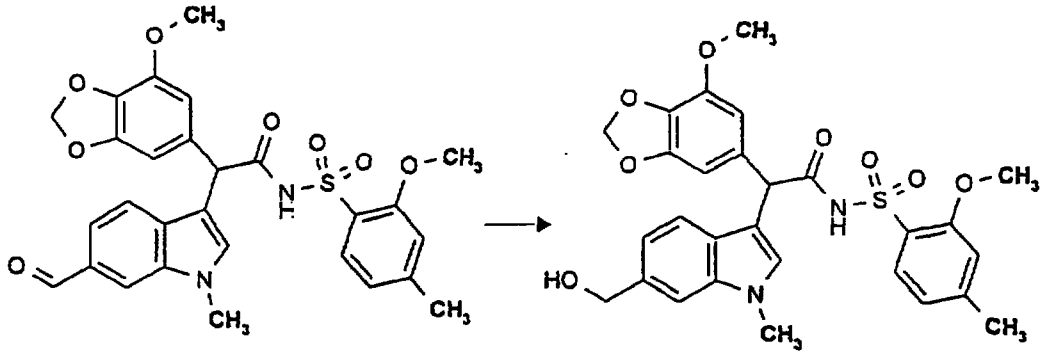
Using 6-bromo-3-{1-(6-chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole (from Example 93) the title compound was prepared in a similar way to Example 96.

^{1}H NMR (300MHz, $CDCl_3$): δ = 2.44 (s, 3H), 3.82 (s, 3H), 5.41 (s, 1H), 5.90 (d, 2H), 6.48 (s, 1H), 6.83 (s, 1H), 7.16 (s, 1H), 7.20-7.33 (m, 3H), 7.50 (d, 1H), 7.82 (s, 1H), 7.85 (d, 2H), 8.40 (brs, 1H exchangeable), 10.02 (s, 1H).

LRMS (APCI): 524.9 (MH^+)

Example 98

6-(Hydroxymethyl)-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



Sodium borohydride (9mg) was added to a suspension of 6-formyl-3-{1-(7-methoxy-1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole (from Example 96, 130mg, 0.24mmol) in a mixture of ethanol (3ml) and 1,4-dioxane (3ml) at ambient temperature. Stirring was continued for 1.5 hours, and then water was added dropwise until a solution was achieved. After carefully acidifying with drops of concentrated hydrochloric acid, the solvents were evaporated in vacuo. The residue was partitioned between ethyl acetate and water, and the organic layer was separated and rewashed with water. The organic layer was dried (magnesium sulphate) and the solvents removed in vacuo. The residue was crystallised from a mixture of methanol and diethyl ether to give the title compound (105mg).

^{1}H NMR (300MHz, d_6-DMSO): δ = 2.35 (s, 3H), 3.60 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 4.56 (d, 2H), 5.02 (t, 1H exchangeable), 5.16 (s, 1H), 5.92 (s, 2H), 6.39 (s, 1H), 6.48 (s, 1H), 6.82-6.98 (m, 4H), 7.16 (d, 1H), 7.30 (s, 1H), 7.66 (d, 1H), 12.20 (s, 1H exchangeable).

LRMS (Thermospray): 553.6 (MH^-)

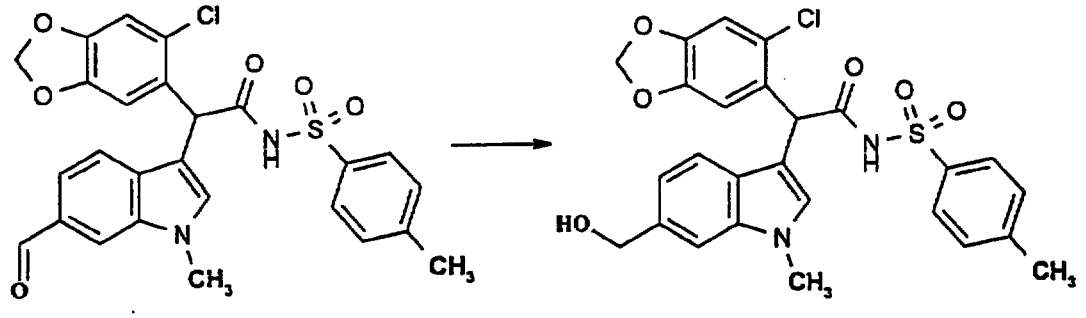
Analysis: Found: C, 60.34; H, 5.43; N, 4.71.

$C_{28}H_{28}N_2O_8S$: Requires: C, 60.86; H, 5.11; N, 5.07.

m.p.: 145-147^{0}C

Example 99

3-{1-(6-Chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(hydroxymethyl) -1-methyl-1*H*-indole



Using 3-{1-(6-Chloro-1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-6-formyl-1-methyl-1*H*-indole from Example 97, the title compound was prepared by the method of Example 98.

^{1}H NMR (300MHz, d_6-DMSO): δ = 2.40 (s, 3H), 3.70 (s, 3H), 4.56 (d, 2H), 5.05 (t, 1H exchangeable), 5.42 (s, 1H), 5.92 (s, 1H), 5.96 (s, 1H), 6.32 (s, 1H), 6.66 (s, 1H), 6.90 (d, 1H), 7.03 (s, 1H), 7.09 (d, 1H), 7.36 (s, 1H), 7.40 (d, 2H), 7.73 (d, 2H), 12.22 (s, 1H exchangeable).

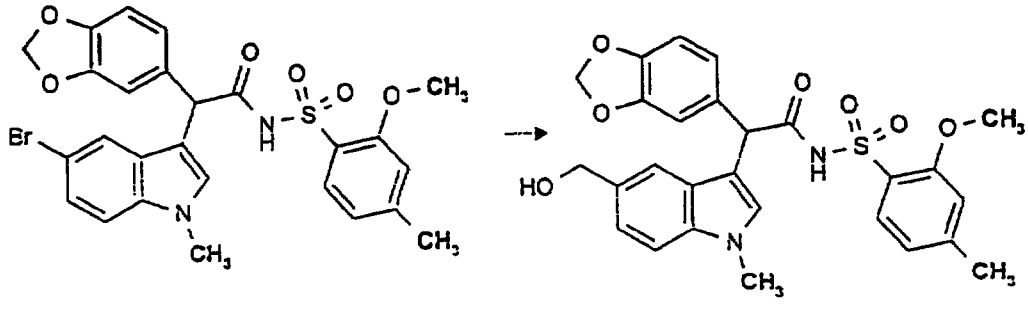
LRMS (APCI): 527.3 (MH^+)

(Thermospray): 544.3 (MNH_4^+)

m.p.: 207-209^{0}C

Example 100

3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-5-(hydroxymethyl)-1-methyl-1*H*-indole



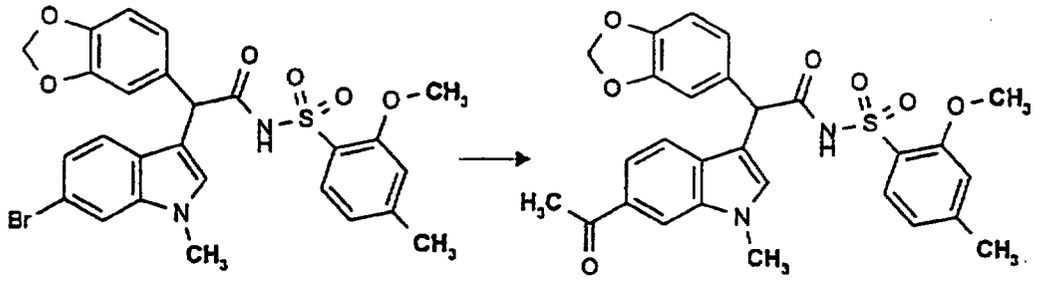
To a solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-5-bromo-1-methyl-1*H*-indole (from Example 79, 300mg, 0.53mmol) in 1,4-dioxane (1.5ml) under a nitrogen atmosphere was added hydroxymethyltributylstannane (253mg, 0.79mmol), followed by tetrakis(triphenylphosphine)palladium(0) (30mg). The mixture was heated to reflux for 8 hours, and then cooled. Sodium hydroxide solution (1M) was added and the mixture boiled to dissolve the product. The solution was decanted clear of an insoluble tar residue, and washed with diethyl ether. After acidification with concentrated hydrochloric acid, the aqueous mixture was extracted with ethyl acetate. The organic extract was dried (magnesium sulphate) and the solvents were evaporated in vacuo. The residue was flash chromatographed using 2% methanol in dichloromethane as eluant to give the title compound (35mg).

^{1}H NMR (300MHz, d_6-DMSO): δ = 2.35 (s, 3H), 3.58 (s, 3H), 3.68 (s, 3H), 4.47 (d, 2H), 4.95 (t, 1H exchangeable), 5.20 (s, 1H), 5.92 (d, 2H), 6.65-7.00 (m, 6H), 7.08 (d, 1H), 7.22 (s, 1H), 7.30 (d, 1H), 7.65 (d, 1H), 12.40 (s, 1H exchangeable).

LRMS (Thermospray): 540.0 (MNH_4^+)

Example 101

6-Acetyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



A mixture of 3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole (from Example 85, 300mg, 0.53mmol), ethyl vinyl ether (0.063ml), palladium(II)acetate (6mg), tri-*o*-tolylphosphine (13mg) and triethylamine (0.1ml) in acetonitrile (5ml) was heated at reflux for 18 hours under a nitrogen atmosphere. After cooling, the solvent was evaporated in vacuo and the residue was stirred with 2N hydrochloric acid (~6ml) for 45 minutes. The mixture was twice extracted with ethyl acetate, and then washed with water, and brine. The organic layer was

dried (magnesium sulphate) and the solvents were evaporated in vacuo. The residue was flash chromatographed using a gradient elution of a mixture of 90% hexane and 10% ethyl acetate, through to 40% hexane and 60% ethyl acetate, to give the title compound (80mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.38 (s, 3H), 2.60 (s, 3H), 3.42 (s, 3H), 3.70 (s, 3H), 5.00 (s, 1H), 5.89 (s, 2H), 6.55 (s, 1H), 6.60-6.70 (m, 3H), 6.83 (d, 1H), 7.03 (s, 1H), 7.21 (d, 1H), 7.55 (d, 1H), 7.90 (m, 2H), 8.80 (s, 1H, exchangeable).

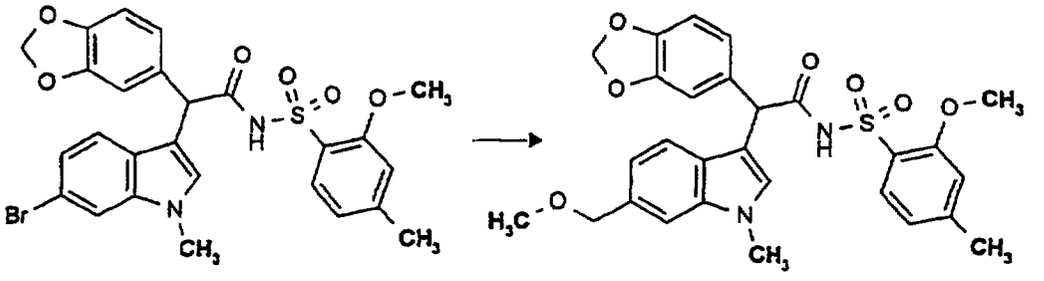
LRMS (APCI): 534.7 (MH^-)

Analysis: Found: C, 60.20; H, 4.84; N, 4.83.

$C_{28}H_{26}N_2O_7S$; 0.4 CH_2Cl_2 Requires: C, 60.00; H, 4.75; N, 4.93.

Example 102

3-{1-(1,3-Benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-(methoxymethyl)-1-methyl-1*H*-indole



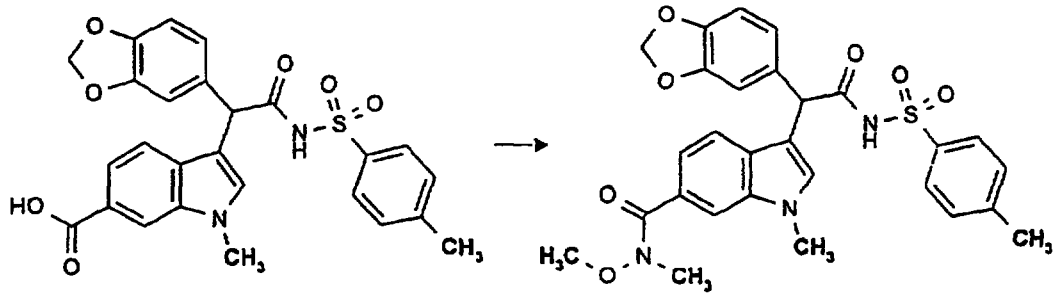
To a solution of 3-{1-(1,3-benzodioxol-5-yl)-2-[(2-methoxy-4-methylphenyl)sulfonamido]-2-oxoethyl}-6-bromo-1-methyl-1*H*-indole (from Example 85, 300mg, 0.53mmol) in 1,4-dioxane (1.5ml) under a nitrogen atmosphere was added methoxymethyltributylstannane (220mg, 0.66mmol), followed by tetrakis(triphenylphosphine)palladium(0) (35mg). The mixture was heated to reflux for 16 hours, and then cooled. An additional portion of tetrakis(triphenylphosphine)palladium(0) (30mg) was added, and reflux was continued for a further 8 hours. The solvent was removed in vacuo, and the residue was flash chromatographed using a gradient elution of a mixture of 1% methanol and 99% dichloromethane, through to 5% methanol and 95% dichloromethane, to give the title compound (33mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.38 (s, 3H), 3.40 (s, 3H), 3.65 (s, 3H), 4.53 (s, 2H), 4.99 (s, 1H), 5.88 (s, 2H), 6.57 (s, 1H), 6.62-6.71 (m, 3H), 6.83 (s, 1H), 6.84 (d, 1H), 6.92 (d, 1H), 7.15 (d, 1H), 7.25 (s, 1H), 7.90 (d, 1H), 8.77 (s, 1H, exchangeable).

LRMS (APCI): 536.9 (MH^-)

Example 103

***N*6-Methoxy-*N*6,1-dimethyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)-sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide**



6-Bromo-1-methylindole was treated according to the method of Example 65(a), but using (4-methylphenyl)sulphonamide in place of the sulphonamide of Preparation 11, to give the methyl ester, which was then treated by the method of Example 4 to give the corresponding acid, which was then converted to the title compound by the method of Example 5 using $(CH_3O)CH_3NH$.

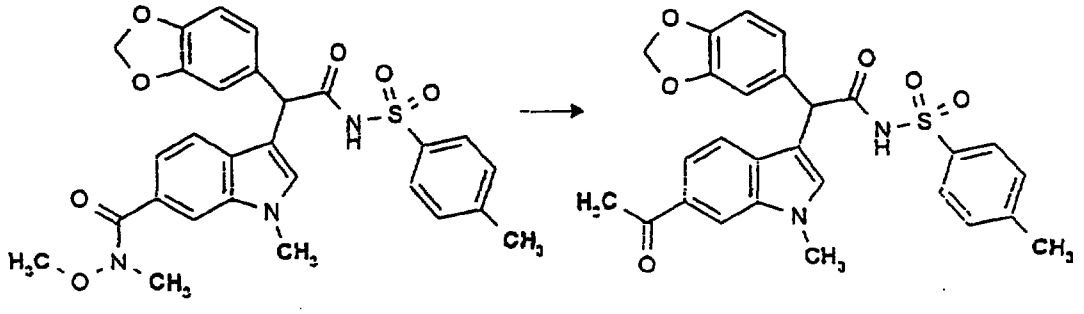
^{1}H NMR (400MHz, $CDCl_3$): δ = 2.47 (s, 3H), 3.42 (s, 3H), 3.59 (s, 3H), 3.75 (s, 3H), 4.98 (s, 1H), 5.93 (s, 2H), 6.65-6.77 (m, 3H), 6.89 (s, 1H), 7.02 (d, 1H), 7.22-7.34 (m, 3H), .7.72 (s, 1H), 7.82 (d, 2H), 8.55 (brs, 1H exchangeable).

Analysis: Found: C, 59.14; H, 4.84; N, 7.35.

$C_{28}H_{27}N_2O_7S$; 0.6 CH_2Cl_2; Requires: C, 59.11; H, 4.84; N, 7.31.

Example 104

6-Acetyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-1*H*-indole



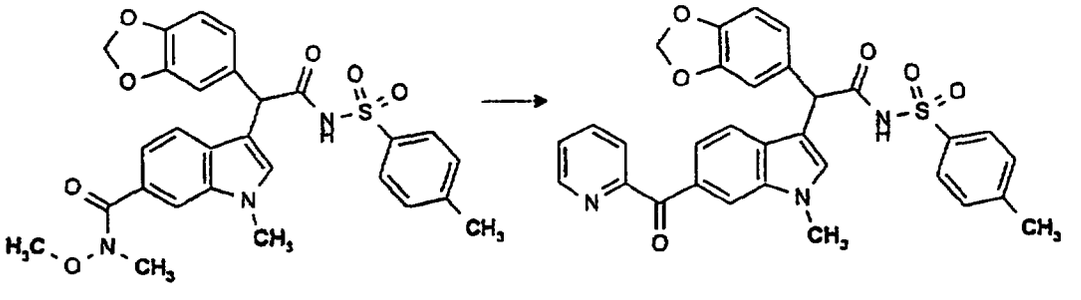
Methylmagnesium bromide (0.23ml of a 3M solution in diethyl ether) was added dropwise to a stirred solution of *N*6-methoxy-*N*6,1-dimethyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide (from Example 103, 174mg, 0.32mmol) in anhydrous tetrahydrofuran (5ml) at -70°C under a nitrogen atmosphere. The mixture was stirred at -70°C for an additional 2 hours before warming to room temperature. Aqueous hydrochloric acid (5ml of 1M solution) was slowly added to the mixture, and then it was extracted with ethyl acetate (100ml). The organic phase was separated and washed with brine, dried (magnesium sulphate) and the solvent were removed in vacuo. The residue was flash chromatographed using a gradient elution of a mixture of 90% hexane and 10% ethyl acetate, through to 100% ethyl acetate, to give the title compound (18mg).

^{1}H NMR (400MHz, d_6-DMSO): δ = 2.30 (s, 3H), 2.56 (s, 3H), 3.73 (s, 3H), 4.90 (s, 1H), 5.87 (d, 2H), 6.65-6.77 (m, 3H), 7.12 (s, 1H), 7.17-7.23 (m, 3H), 7.44 (d, 1H), 7.60 (d, 2H), 7.97 (s, 1H), 12.40 (brs, 1H exchangeable).

LRMS (Thermospray): 506.0 (MH^+), 522.6 (MNH_4^+)

Example 105

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-6-(2-pyridylcarbonyl)-1*H*-indole



n-Butyllithium (0.32ml of 2.5M solution in hexane) was added to a stirred solution of 2-bromopyridine (0.08ml, 0.8mmol) in anhydrous tetrahydrofuran (5ml) at -70°C under a nitrogen atmosphere. After 30 minutes a solution of *N*6-methoxy-*N*6,1-dimethyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide (the compound of Example 103, 200mg, 0.36mmol) in anhydrous tetrahydrofuran (2ml) was added to the mixture at -70°C. The mixture was stirred at -70°C for an additional 4 hours before being warmed to 0°C, and then quenched with the addition of water (5ml).

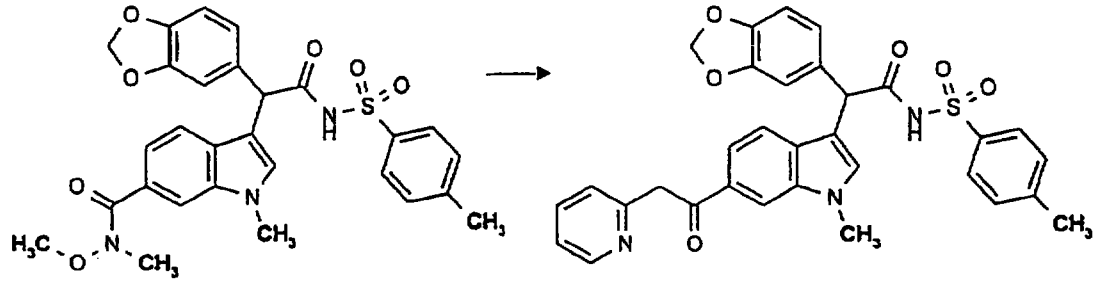
The mixture was acidified with acetic acid. and extracted with ethyl acetate (100ml). The organic phase was separated and washed with brine. dried (magnesium sulphate) and the solvent was removed in vacuo. The residue was flash chromatographed using a gradient elution of a mixture of 90% hexane and 10% ethyl acetate. through to 100% ethyl acetate. to give the title compound (42mg).

^{1}H NMR (400MHz. $CDCl_3$): δ = 2.42 (s, 3H). 3.73 (s. 3H). 4.98 (s. 1H). 5.91 (s. 2H). 6.60-6.70 (m. 3H). 6.98 (s. 1H). 7.10 (d. 1H). 7.27 (d. 2H). 7.48 (dd. 1H). 7.62 (d. 1H). 7.81 (d. 2H). 7.90 (dd. 1H). 8.00 (d. 1H). 8.10 (s. 1H). 8.72 (d. 1H).

LRMS (APCI): 568.3 (MH^+)

Example 106

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-methyl-6-[2-(2-pyridyl)acetyl]-1*H*-indole



Lithium diisopropylamide mono(tetrahydrofuran) (0.53ml of 1.5M solution in cyclohexane) was added to a stirred solution of 2-methylpyridine (0.08ml, 0.8mmol) in anhydrous tetrahydrofuran (3ml) at -70°C under a nitrogen atmosphere. After 20 minutes a solution of *N*6-methoxy-*N*6.1-dimethyl-3-{1-(1.3-benzodioxol-5-yl)-2-[(4-methylphenyl)-sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide (the compound of Example 103, 200mg, 0.36mmol) in anhydrous tetrahydrofuran (2ml) was added to the mixture at -70°C. The mixture was stirred at -70°C for an additional 2 hours before being warmed to 0°C. and then quenched with the addition of water (5ml). The mixture was acidified with acetic acid. and extracted with ethyl acetate (100ml). The organic phase was separated and washed with brine. dried (magnesium sulphate) and the solvent was removed in vacuo. The residue was flash chromatographed using a gradient elution of a mixture of 90% hexane and 10% ethyl acetate. through to 100% ethyl acetate. to give the title compound (95mg).

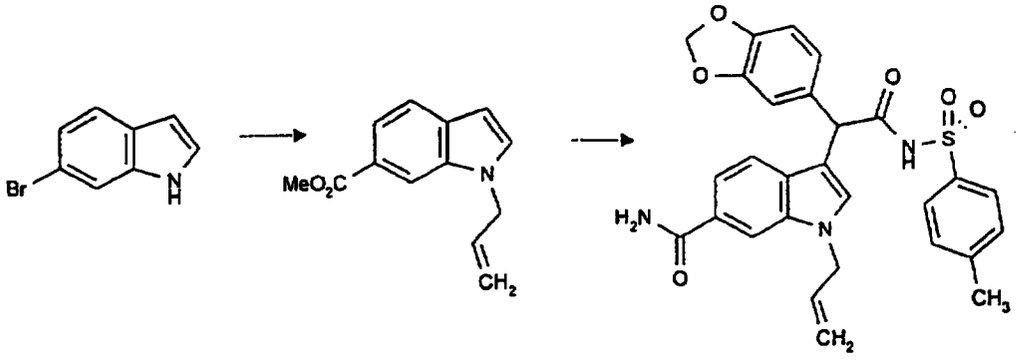
^{1}H NMR (400MHz, d_6-DMSO): Complex due to keto and enol forms of the (2-pyridyl)acetyl group of the compound.

^{1}H NMR (300MHz, TFA-d): δ = 2.43 (s, 3H), 3.79 (s, 3H), 5.21 (s, 1H), 5.90 (s, 2H), 6.62 (s, 1H), 6.66 (d, 1H), 6.75 (d, 1H), 7.02 (s, 1H), 7.30-7.40 (m, 3H), 7.70 (d, 1H), 7.81 (d, 2H), 7.96-8.08 (m, 2H), 8.13 (s, 1H), 8.59 (dd, 1H), 8.78 (d, 1H), 11.5 (exchanged NH, and the CH_2 of (2-pyridyl)acetyl group).

LRMS (APCI): 582.7 (MH^+)

Example 107

1-Allyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide



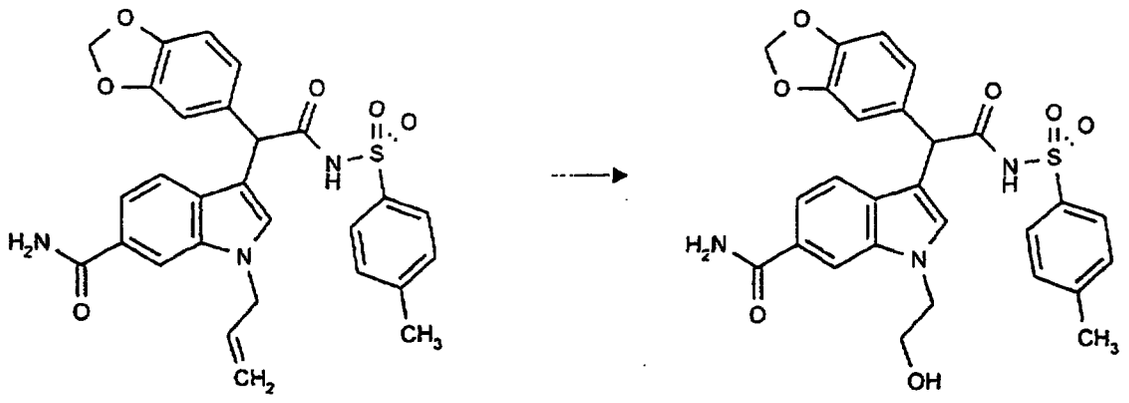
The title compound was prepared from 6-bromo-1-ethylindole using the methods of Examples 1(a) (but using allyl bromide in place of ethyl bromide), 1(b), 1(d), 2, 3 (but using (4-methylphenyl)sulphonamide), 4 and 12.

^{1}H NMR (300MHz, CD_3OD): δ = 2.40 (s, 3H), 4.65 (d, 2H), 4.95 (d, 1H), 5.00 (s, 1H), 5.10 (d, 1H), 5.80 (d, 2H), 5.95 (m, 1H), 6.70 (m, 3H), 6.95 (s, 1H), 7.10 (s, 1H), 7.20 (d, 2H), 7.40 (d, 1H), 7.70 (d, 2H), 7.80 (s, 1H).

LRMS (Thermospray): 549.3 (MNH_4^-).

Example 108

3-{1-(1,3-Benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1-(2-hydroxyethyl)-1*H*-6-indolecarboxamide



Osmium tetroxide (239mg, 0.94 mmol), pyridine (0.225 ml, 4.7 mmol) and N-methylmorpholine N-oxide (549 mg, 2.84 mmol) were added to a stirred solution of 1-allyl-3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methylphenyl)sulfonamido]-2-oxoethyl}-1*H*-6-indolecarboxamide (the compound of Example 107) in aqueous tetrahydrofuran (10ml tetrahydrofuran : 1ml H_2O) at room temperature. After 4h a solution of sodium thiosulphate (10ml) was added and stirring continued for 1h. The black precipitate was removed by filtration through celite and the solvent removed in vacuo. The crude diol was redissolved in ethyl acetate (50ml) and washed with 1M hydrochloric acid (50ml) then brine (50ml). The organic layer was dried ($MgSO_4$) and concentrated to give a brown solid. Sodium metaperiodate (1.0g, 4.7mmol) dissolved in water (1ml) was added to a stirred slurry of the brown solid in ethyl acetate (10ml). After 2h the mixture was filtered, diluted with ethyl acetate (50 ml) and washed with saturated sodium chloride solution. The organic layer was dried (magnesium sulphate) and concentrated in vacuo Partial purification was undertaken at this stage by flash column chromatography (elution with 90% dichloromethane /10% methanol) giving an aldehyde intermediate as a fawn solid.

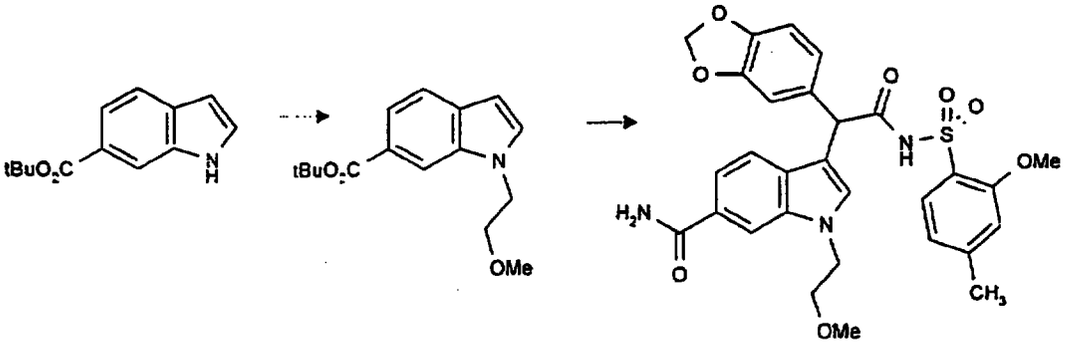
Without further purification this solid was dissolved in methanol (15ml) at room temperature under a nitrogen atmosphere. Sodium borohydride (36mg) was added portionwise over 10 minutes and stirring was continued for 4h. The methanol was removed in vacuo and the residue redissolved in ethyl acetate (50ml). The ethyl acetate solution was washed with saturated aqueous NH_4Cl (50 ml), dried ($MgSO_4$) and concentrated to give a yellow foam. Flash column chromatography (elution with 90% dichloromethane/10% methanol) gave the product as a fawn solid (126mg).

^{1}H NMR (300MHz. d_6-DMSO): δ = 2.40 (s. 3H). 3.60 (m. 2H). 4.10 (m. 2H). 5.10 (s. 1H). 5.90 (s. 1H). 6.65 (s. 1H). 6.70 (d. 1H). 6.80 (d. 1H). 7.10 (s. 1H). 7.15 (d. 1H). 7.30 (d. 2H). 7.40 (d. 1H). 7.70 (d. 2H). 8.00 (s. 1H).

LRMS (APCI): 536.2 (MH^+).

Example 109

3-{1-(1,3-benzodioxol-5-yl)-2-[(4-methyl-2-methoxyphenyl)sulfonamido]-2-oxoethyl}-1-(2-methoxyethyl)-1*H*-6-indolecarboxamide



The title compound was prepared from the compound of Example 28(b) using the methods of Examples 28(c) (but using $CH_3OCH_2CH_2Br$ in place of methyl iodide), 28(d), 28(e), 28(f) and 28(g) (but using the sulphonamide of Preparation 11 in place of p-toluenesulphonamide).

^{1}H NMR (300MHz. d_6-DMSO): δ = 2.35 (s. 3H). 3.20 (s. 3H). 3.60 (m. 2H). 3.65 (s. 3H). 4.20 (m. 2H). 5.20 (s. 1H). 5.95 (s. 2H). 6.70 (s. 1H). 6.75 (d. 1H). 6.80 (d. 1H). 6.85 (d. 1H). 6.90 (s. 1H). 7.15 (s. 1H). 7.20 (d. 1H). 7.45 (d. 1H). 7.60 (d. 1H). 7.80 (brs. 1H). 8.00 (s. 1H).

LRMS (Thermospray): 580.8 (MH^+).

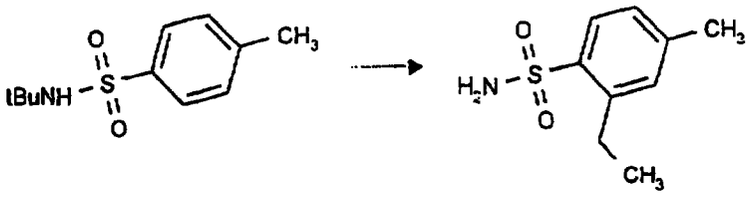
Example 110

The compounds of Examples 17. 50. 65. 83 101 and 109 were tested in Test A above. and found to have an $IC_{50}(ET_A)$ < 500nM. and a selectivity for ET_A receptors over ET_B receptors of greater than 100.

The preparation of some aromatic sulphonamides is described below.

Preparation 1

2-Ethyl-4-methyl-1-benzenesulfonamide



n-Butyllithium (5.3ml of 2.5M in hexane solution) was added to a stirred solution of *N*1-(*tert*-butyl)-2-ethyl-4-methyl-1-benzenesulfonamide (1g, 4.45mmol) in tetrahydrofuran (30ml) at 0°C under a nitrogen atmosphere. After 2h bromoethane was added dropwise. After 4h the reaction mixture was poured into aqueous ammonium chloride and the product was extracted with ethyl acetate (2 x 100ml). The combined organic fractions were washed with brine (100ml), dried ($MgSO_4$) and concentrated in vacuo. A mixture of ethyl acetate (8ml) and hexane (2ml) was added and a white solid crystallised (450mg).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.20 (s, 9H), 1.30 (t, 3H), 2.40 (s, 3H), 3.00 (q, 2H), 4.40 (s, 1H), 7.00 (d, 1H), 7.10 (s, 1H), 7.80 (d, 1H).

LRMS (Thermospray): 256.4 (MH^+).

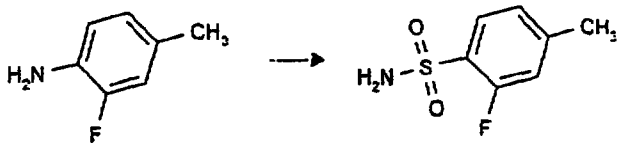
Polyphosphoric acid (approx. 10ml) was added to this white solid and the slurry was heated at 100°C for 30mins. The yellow solution was then carefully poured into iced water (100ml) and extracted with ethyl acetate (2 x 100ml). The organic layers were dried ($MgSO_4$) and concentrated. The product was purified by flash column chromatography (gradient elution from dichloromethane to 5%methanol/dichloromethane) giving the desired sulphonamide as a white solid.

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.30 (t, 3H), 2.40 (s, 3H), 3.00 (q, 2H), 4.80 (brs, 2H), 7.05 (d, 1H), 7.20 (s, 1H), 7.80 (d, 1H).

LRMS (Thermospray): 216.5 (MNH_4^+).

Preparation 2

2-Fluoro-4-methyl-1-benzenesulfonamide



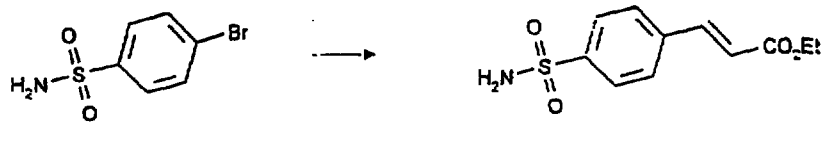
2-Fluoro-4-methylaniline (3g, 24mmol) was dissolved in glacial acetic acid (45ml) and concentrated hydrochloric acid (15ml) and the solution was cooled to -10°C with overhead stirring. Sodium nitrite (1.82g, 26.4 mmol) in water (3ml) was added dropwise over 0.5h maintaining the temperature below -5°C. Stirring was continued for a further 0.5h after the final addition. This mixture was added in small portions to a stirred, saturated solution of sulphur dioxide in acetic acid (30ml) at 0°C. After addition the mixture was warmed to room temperature and stirred for 1h before pouring into iced water. After stirring for 0.5h the product was extracted into ether and the aqueous layer further extracted with dichloromethane. The organic layers were combined, washed with brine, dried ($MgSO_4$) and concentrated (azeotroping with toluene to remove any remaining acetic acid). A mixture of 1,4-dioxan (30ml) and aqueous ammonia (30ml of 0.88M) was added to the residue which was stirred overnight. The 1,4-dioxan was removed in vacuo and the aqueous layer extracted with ethyl acetate (2 x 100ml). The organic layers were combined, washed with brine (100ml), dried ($MgSO_4$) and concentrated. Flash column chromatography (elution with 99% dichloromethane /1% methanol) gave the product as a pale yellow solid (1.62g).

^{1}H NMR (400MHz, $CDCl_3$): δ = 1.30 (t, 3H), 2.40 (s, 3H), 3.00 (q, 2H), 4.80 (brs, 2H), 7.05 (d, 1H), 7.20 (s, 1H), 7.80 (d, 1H).

LRMS (APCI): 216.5 (MNH_4^+).

Preparation 3

Ethyl (*E*)-3-(4-sulfamoylphenyl)-2-propenoate



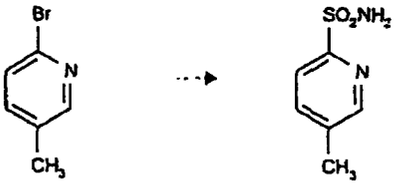
The title compound was prepared by the method of Example 57 from the starting material shown.

^{1}H NMR (400MHz. CD_3OD): δ = 1.40 (t. 3H). 4.25 (q. 2H). 6.60 (d. 1H). 7.70 (d. 1H). 7.75 (d. 2H). 7.90 (d. 2H).

LRMS (Thermospray): 272.9 (MNH_4^+).

Preparation 4

5-Methyl-2-pyridinesulfonamide



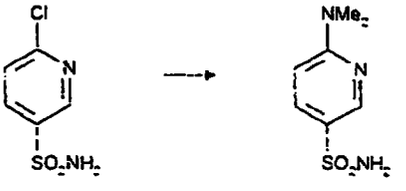
Sec-butyllithium (9.8ml of 1.3M in cyclohexane) and N,N,N',N'-tetramethylethylenediamine (1.8ml. 12.2mmol) were added to a stirred solution of 2-bromo-5-methylpyridine (2g, 11.6mmol) at -78°C under a nitrogen atmosphere. After 90 min sulphur dioxide (approximately 30ml) was condensed into the reaction mixture using a cold finger and the reaction mixture was slowly warmed to room temperature over 12h. The reaction mixture was concentrated to dryness and the residue dissolved in ice-water. To this was added a mixture of sodium hydroxide (1.39g, 35mmol) and hydroxylamine sulphonic acid (3.9g, 35mmol) in water (20ml). After 24h the solution was extracted with ethyl acetate. dried ($MgSO_4$) and concentrated. Flash column chromatography (95% dichloromethane /5% methanol) gave the product (250mg) as a clear oil which crystallised on standing.

^{1}H NMR (400MHz. $CDCl_3$): δ = 2.40 (s, 3H), 5.20 (brs. 2H), 7.80 (d. 1H), 7.90 (d, 1H), 8.50 (s, 1H).

LRMS (Thermospray): 172.8 (MH^+).

Preparation 5

6-(Dimethylamino)-3-pyridinesulfonamide



Chlorosulphonamide (500mg) was dissolved in ethanol (5ml) and dimethylamine (15ml of a 2M solution in tetrahydrofuran). The reaction mixture was sealed in a pressure bomb and heated at 100°C for 12h. The mixture was cooled and the solvent removed in vacuo. Flash column chromatography (elution with 95% dichloromethane/5% methanol) gave the product (550mg) as a pale orange solid.

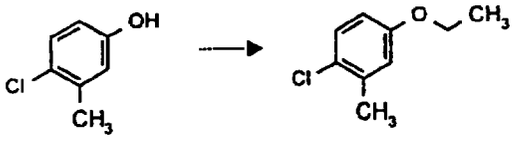
^{1}H NMR (400MHz. $CDCl_3$): δ = 3.20 (s. 6H). 4.80 (brs, 2H). 6.50 (d. 1H), 7.80 (d. 1H). 8.65 (s, 1H).

LRMS (Thermospray): 202.2 (MH^+).

Preparation 6

5-Chloro-2-ethoxy-4-methyl-1-benzenesulfonamide

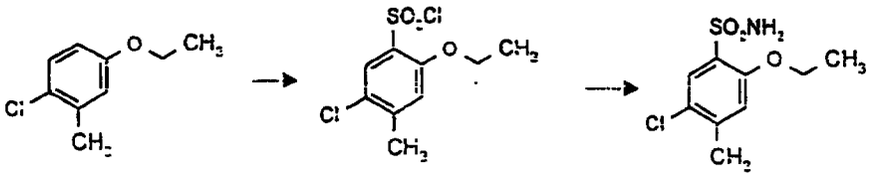
(a) 1-Chloro-4-ethoxy-2-methylbenzene



To a solution of 1-chloro-4-hydroxymethylbenzene (14.2g, 0.1mol) in tetrahydrofuran (250ml) was added sodium hydride as a 40% suspension in oil (4g, 0.1mol) portionwise under nitrogen. When effervescence ceased iodoethane (15.6g, 0.1mol) was added and the solution heated at reflux for 8 hours. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with dilute aqueous sodium hydroxide and brine, then dried ($MgSO_4$) and evaporated to dryness. The subtitle compound was obtained as a clear oil (17.3g).

^{1}H NMR (300MHz $CDCl_3$): δ = 1.40 (t, 3H). 2.35 (s. 3H), 4.00 (q, 2H). 6.65 (dt, 1H). 6.75 (d, 1H), 7.20 (d. 1H).

(b) 5-Chloro-2-ethoxy-4-methyl-1-benzenesulfonamide



To 1-chloro-4-ethoxy-2-methylbenzene (from step (a). 17g) was added chlorosulphonic acid (25ml) dropwise with stirring and ice cooling. The solution was stirred for 30 minutes then poured onto ice (200ml) and the crude intermediate sulphonyl chloride filtered off. This material was mixed thoroughly with ammonium carbonate solid (35g) and heated at 100°C for 30 minutes. The mixture was cooled and poured into ice water then filtered off and crystallised from hot ethyl acetate (15.2g). m.p. 153-5°C.

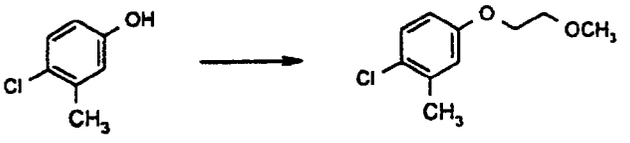
^{1}H NMR (300MHz, d_6-DMSO): δ = 1.40 (t. 3H). 2.40 (s. 3H). 4.20 (q. 2H), 7.00 (s. 2H), 7.25 (s, 1H). 7.60 (s, 1H).

LRMS (Thermospray): 267.5 (MNH_4^+).

Preparation 7

5-Chloro-2-(2-methoxyethoxy)-4-methyl-1-benzenesulfonamide

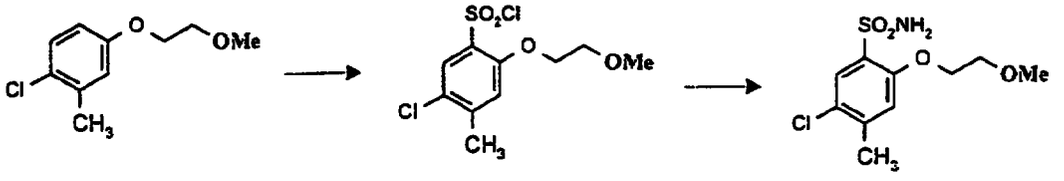
(a) 1-Chloro-4-(2-methoxyethoxy)-2-methylbenzene



The subtitle compound was prepared using the method of Preparation 6(a), but using $CH_3OCH_2CH_2Br$ in place of iodoethane.

^{1}H NMR (300MHz $CDCl_3$): δ = 2.35 (s, 3H). 3.45 (s. 3H). 3.75 (t. 2H). 4.05 (t.2H), 6.70 (dd. 1H). 6.80 (d, 1H), 7.20 (d, 1H).

(b) **5-Chloro-2-(2-methoxyethoxy)-4-methyl-1-benzenesulfonamide**



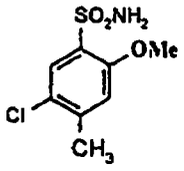
The title compound was prepared from the product of step (a) by the method of Preparation 6(b).

^{1}H NMR (300MHz $CDCl_3$): δ = 2.40 (s. 3H). 3.45 (s. 3H). 3.80 (t. 2H). 4.25 (t.2H). 5.45 (s, 2H). 6.85 (s. 1H). 7.90 (s. 1H).

LRMS (Thermospray): 297.1 (MNH_4^-).

Preparation 8

5-Chloro-2-methoxy-4-methyl-1-benzenesulfonamide



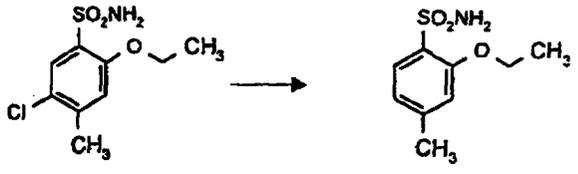
The title compound was prepared by the method of Preparation 6. but using iodomethane in place of iodoethane.

^{1}H NMR (300MHz $CDCl_3$): δ = 2.40 (s, 3H), 4.00 (s. 3H), 5.00 (s. 2H). 6.90 (s, 1H), 7.85 (s, 1H).

LRMS (Thermospray): 252.9 (MNH_4^+).

Preparation 9

2-Ethoxy-4-methyl-1-benzenesulfonamide



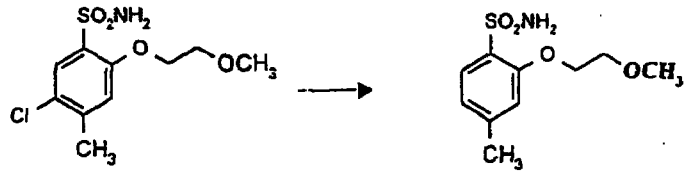
To a solution of the chlorosulphonamide from Preparation 6 (5.0g) in ethanol (25ml) and water (25ml) was added Raney nickel (4g of a 50% suspension in water) and the mixture heated at reflux for 24 hours. Hot methanol (100ml) was added and the reducing agent removed by filtration. Solvents were evaporated and the residue crystallised from hot ethanol (2.42g). m.p.136-7°C.

^{1}H NMR (300MHz. d_6-DMSO): δ = 1.40 (t. 3H), 2.35 (s. 3H), 4.20 (q. 2H), 6.75 (s. 2H), 6.80 (d, 1H), 7.00 (s, 1H). 7.60 (d, 1H).

LRMS (Thermospray): 233.5 (MNH_4^+).

Preparation 10

2-(2-Methoxyethoxy)-4-methyl-1-benzenesulfonamide



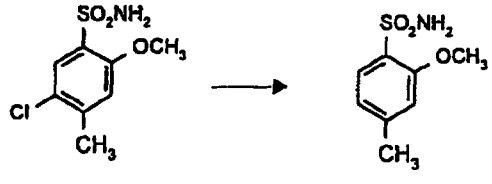
The title compound was prepared by the method of Preparation 9 from the product of Preparation 7.

^{1}H NMR (300MHz $CDCl_3$): δ = 2.40 (s. 3H), 3.45 (s, 3H), 3.80 (t, 2H). 4.25 (t,2H), 5.20 (s, 2H), 6.80 (s, 1H). 6.90 (d. 1H), 7.80 (d, 1H).

LRMS (Thermospray): 246 (MH^+).

Preparation 11

2-Methoxy-4-methyl-1-benzenesulfonamide



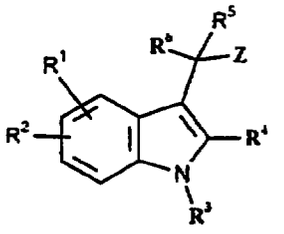
The title compound was prepared by the method of Preparation 9 from the product of Preparation 8.

^{1}H NMR (300MHz $CDCl_3$): δ = 2.40 (s, 3H), 4.00 (s, 3H), 5.00 (brs, 2H), 6.80 (m, 2H), 7.80 (d, 1H).

LRMS (Thermospray): 219.0 (MNH_4^+)

Claims:

1. A compound of formula I.



I

wherein

R^1 and R^2 are optional substituents and independently represent C_{1-6} alkyl, C_{2-6} alkenyl [optionally substituted by CO_2H or $CO_2(C_{1-6}$ alkyl)], C_{2-6} alkynyl, halogen, C_{1-3} perfluoroalkyl, $(CH_2)_mAr^1$, $(CH_2)_mHet^1$, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $O(CH_2)_qCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$, $O(CH_2)_pOR^8$, $(CH_2)_mNR^7R^8$, $CO_2(CH_2)_qNR^7R^8$, $(CH_2)_mCN$, $S(O)_nR^8$, $SO_2NR^7R^8$, $CONH(CH_2)_mAr^1$ or $CONH(CH_2)_mHet^1$;

R^3 represents H, C_{1-6} alkyl, $(CH_2)_pNR^9R^{10}$, SO_2R^{10}, $SO_2NR^9R^{10}$, $(CH_2)_mCOR^{10}$, C_{2-6} alkenyl, C_{2-6} alkynyl, $(CH_2)_mCONR^9R^{10}$, $(CH_2)_mCO_2R^{10}$, $(CH_2)_pCN$, $(CH_2)_pR^{10}$ or $(CH_2)_pOR^{10}$;

R^4 and R^9 independently represent H or C_{1-6} alkyl;

R^7 represents H, C_{1-6} alkyl or C_{1-6} alkoxy;

R^5 represents H or OH;

R^6 represents phenyl optionally fused to a saturated or unsaturated 5- or 6-membered heterocyclic ring containing 1 or 2 heteroatoms selected from N, S and O, the group as a whole being optionally substituted by one or more groups selected from C_{1-6} alkyl, C_{1-6} alkoxy and halogen, and wherein any members of the heterocyclic ring which are S may be substituted by one or two oxygen atoms;

R^8 and R^{10} independently represent H, C_{1-6} alkyl, Ar^2, Het^2 or C_{1-6} alkyl substituted by Ar^2 or Het^2;

Z represents CO_2H, CONH(tetrazol-5-yl), $CONHSO_2O(C_{1-4}$ alkyl), CO_2Ar^3, $CO_2(C_{1-6}$ alkyl), tetrazol-5-yl, $CONHSO_2Ar^3$, $CONHSO_2(CH_2)_qAr^3$ or $CONHSO_2(C_{1-6}$ alkyl);

m represents 0, 1, 2 or 3;

n represents 0, 1 or 2;

p represents 2, 3 or 4;

q represents 1, 2 or 3;

Ar^{1-3} independently represent phenyl, naphthyl, or an aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which aromatic heterocycle is optionally fused to a benzene ring, and which phenyl group is optionally fused to an aromatic heterocycle as defined immediately above, the group as a whole being optionally substituted by one or more groups falling within the definition of R^1 above; and

Het^1 and Het^2 independently represent a non-aromatic heterocycle having 5 or 6 ring members up to 4 of which are selected from N, S and O, which group is optionally substituted by one or more groups falling within the definition of R^1 above, and is further optionally substituted by =O or =S;

provided that:

(i) when R^1 represents methoxy or is absent, R^2 is absent, R^3 represents H, R^4 represents H, methyl or ethyl, and R^6 represents unsubstituted phenyl, then Z does not represent CO_2H or $CO_2(C_{1-6}$ alkyl);

(ii) when R^1 and R^2 are absent, R^3 represents $CO(p\text{-}ClC_6H_4)$, R^4 represents H, and R^6 represents unsubstituted phenyl, then Z does not represent $CO_2(C_{1-6}$ alkyl); and

(iii) when R^1 represents methoxy, R^2 is absent, R^3 represents $CO(p\text{-}ClC_6H_4)$, R^4 represents methyl, and R^6 represents unsubstituted phenyl, then Z does not represent CO_2H;

or a pharmaceutically acceptable derivative thereof.

2. A compound as claimed in claim 1, wherein R^1 represents halogen, $(CH_2)_mCONR^7R^8$, $(CH_2)_mCO_2R^8$, $(CH_2)_mCOR^8$, $(CH_2)_mOR^8$ or $(CH_2)_mCN$.

3. A compound as claimed in claim 1 or claim 2, wherein R^2 is absent.

4. A compound as claimed in any one of the preceding claims, wherein R^3 represents H, C_{1-6} alkyl or $(CH_2)_pOR^{10}$.

5. A compound as claimed in any one of the preceding claims, wherein R^4 represents H.

6. A compound as claimed in any one of the preceding claims, wherein R^5 represents H.

7. A compound as claimed in any one of the preceding claims, wherein R^6 represents phenyl fused to a saturated 5-membered heterocyclic ring.

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8. A compound as claimed in any one of the preceding claims, wherein Z represents CO_2H or $CONHSO_2Ar^3$.

9. A compound of formula I, as defined in claim 1, but without provisos (i) and (ii), or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.

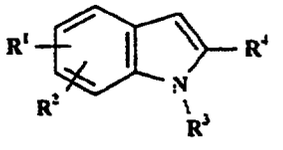
10. A pharmaceutical formulation comprising a compound of formula I, as defined in claim 1, but without provisos (i) and (ii), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable adjuvant, diluent or carrier.

11. Use of a compound of formula I, as defined in claim 1, but without provisos (i)-(iii), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity.

12. A method of treatment of restenosis, renal failure, pulmonary hypertension, benign prostatic hypertrophy, congestive heart failure, stroke, angina, atherosclerosis, cerebral and cardiac ischaemia or cyclosporin induced nephrotoxicity, which comprises administering a therapeutically effective amount of a compound of formula I, as defined in claim 1, but without provisos (i)-(iii), or a pharmaceutically acceptable derivative thereof, to a patient in need of such treatment.

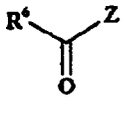
13. A process for the production of a compound of formula I, as defined in claim 1, or a pharmaceutically acceptable derivative thereof, which comprises:

(a) when R^5 represents H, reaction of a compound of formula IIA,



IIA

wherein R^{1-4} are as defined in claim 1, with a compound of formula III,



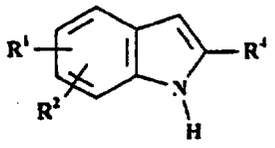
III

wherein R^6 and Z are as defined in claim 1, in the presence of a Lewis acid or trifluoroacetic acid, and a tri(C_{1-6} alkyl)silane;

(b) when R^5 represents OH, reaction of a compound of formula IIA, as defined above, with a compound of formula III, as defined above, in the presence of a Lewis acid:

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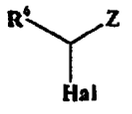
(c) when R^3 represents H and R^5 represents H, treatment of a compound of formula IIB,



IIB

wherein R^1, R^2 and R^4 are as defined in claim 1, with a Grignard reagent, followed by reaction with a compound of formula III, as defined above, followed by treatment with a Lewis acid or trifluoroacetic acid, and a tri(C_{1-6} alkyl)silane;

(d) when R^3 represents H and R^5 represents H, treatment of a compound of formula IIB, as defined above, with a Grignard reagent, followed by reaction with a compound of formula IV,



IV

wherein R^6 and Z are as defined in claim 1, and Hal represents halogen;

(e) when R^5 represents H, reaction of a compound of formula IIA, as defined above, with a compound of formula IV, as defined above, in the presence of a hindered, non-nucleophilic base;

(f) reacting a compound of formula I, in which R^1 represents Br, with CO gas in the presence of a palladium catalyst and a reducing agent, to provide the corresponding compound of formula I in which R^1 represents CHO;

(g) reacting a compound of formula I, in which R^1 represents Br, with CO gas in the presence of a palladium catalyst and a C_{1-6} alkanol, to provide the corresponding compound of formula I in which R^1 represents $CO_2(C_{1-6}$ alkyl);

(h) coupling a compound of formula I, in which Z represents CO_2H, with a compound of formula VI,

$$H_2NSO_2Ar^3 \qquad VI$$

wherein Ar^3 is as defined in claim 1, to provide the corresponding compound of formula I in which Z represents $CONHSO_2Ar^3$; or

(i) reacting a compound of formula I, in which R^1 represents Br, with an alkyl lithium reagent and quenching with dimethylformamide or carbon dioxide to give a corresponding compound in which R^1 represents CHO or CO_2H respectively;

and where desired or necessary converting the resulting compound of formula I into a pharmaceutically acceptable derivative thereof or vice versa.