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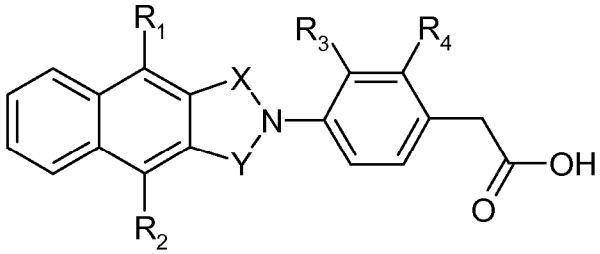
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(54) **Title:** BENZOISOINDOLE DERIVATIVES AND THEIR USE AS EP4 RECEPTOR AGONISTS FOR THE TREATMENT OF PAIN



(I)

(57) **Abstract:** A compound of formula (I) wherein R_1 represents C_{1-4}alkyl or C_{1-4}alkoxy; R_2 represents C_{1-4}alkyl or C_{1-4}alkenyl; R_3 represents H, F, Cl, methyl, methoxy or CF_3; R_4 represents H or F; X represents CH_2 or C=O; and Y represents CH_2 or C=O, provided that at least one of X and Y represents C=O and at least one of R_3 and R_4 is H; and pharmaceutically acceptable derivatives thereof, processes for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds in medicine.

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BENZOISOINDOLE DERIVATIVES AND THEIR USE AS EP4 RECEPTOR AGONISTS FOR THE TREATMENT OF PAIN

This invention relates to naphthalene derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine.

The compounds of the present invention are EP_4 receptor agonists.

A number of review articles describe the characterization and therapeutic relevance of the prostanoid receptors as well as the most commonly used selective agonists and antagonists: *Eicosanoids; From Biotechnology to Therapeutic Applications,* Folco, Samuelsson, Maclouf, and Velo eds, Plenum Press, New York, 1996, chap. 14, 137-154 and Journal of Lipid Mediators and Cell Signalling, 1996, 14, 83-87 and *Prostanoid Receptors, Structure, Properties and Function,* S Narumiya et al, Physiological Reviews 1999, 79(4), 1193-126.

The EP_4 receptor is a 7-transmembrane receptor and its natural ligand is the prostaglandin PGE_2. PGE_2 also has affinity for the other EP receptors (types EP_1, EP_2 and EP_3). The prostanoid EP_4 receptor falls into a group of receptors normally associated with elevation of intracellular cyclic adenosine monophosphate (cAMP) levels. The EP_4 receptor is associated with smooth muscle relaxation, intraocular pressure, pain (in particular inflammatory, neuropathic and visceral pain), inflammation, neuroprotection, lymphocyte differentiation, bone metabolic processes, allergic activities, promotion of sleep, renal regulation, gastric or enteric mucus secretion and duodenal bicarbonate secretion. The EP_4 receptor plays an important role in closure of the ductus arteriosus, vasodepression, inflammation and bone remodeling as reviewed by Narumiya in *Prostaglandins & Other Lipid Mediators* 2002, 68-69 557-73.

A number of publications have demonstrated that PGE_2 acting through the EP_4 receptor subtype, and EP_4 agonists alone, can regulate inflammatory cytokines after an inflammatory stimulus. Takayama *et al* in the *Journal of Biological Chemistry* 2002, 277(46), 44147-54 showed PGE_2 modulates inflammation during inflammatory diseases by suppressing macrophage derived chemokine production via the EP_4

receptor. In *Bioorganic & Medicinal Chemistry* 2002, 10(7), 2103-2110, Maruyama *et al* demonstrate the selective EP_4 receptor agonist (ONO-AE1-437) suppresses LPS induced TNF-α in human whole blood whilst increasing the levels of IL-10. An article from *Anesthesiology,* 2002, 97,170-176 suggests that a selective EP_4 receptor agonist (ONO-AE1-329) effectively inhibited mechanical and thermal hyperalgesia and inflammatory reactions in acute and chronic monoarthritis.

Two independent articles from Sakuma *et al* in *Journal of Bone and Mineral Research* 2000, 15(2), 218-227 and Miyaura *et al* in *Journal of Biological Chemistry* 2000, 275(26), 19819-23, report impaired osteoclast formation in cells cultured from EP_4 receptor knock-out mice. Yoshida *et al* in *Proceedings of the National Academy of Sciences of the United States of America* 2002, 99(7), 4580-4585, by use of mice lacking each of the PGE_2 receptor EP subtypes, identified EP_4 as the receptor that mediates bone formation in response to PGE_2 administration. They also demonstrated a selective EP_4 receptor agonist (ONO-4819) consistently induces bone formation in wild type mice. Additionally, Terai *et al* in *Bone* 2005, 37(4), 555-562 have shown the presence of a selective EP_4 receptor agonist (ONO-4819) enhanced the bone-inducing capacity of rhBMP-2, a therapeutic cytokine that can induce bone formation.

Further research by Larsen *et al* shows the effects of PGE_2 on secretion in the second part of the human duodenum is mediated through the EP_4 receptor (*Acta. Physiol. Scand.* 2005, 185, 133-140). Also, it has been shown a selective EP_4 receptor agonist (ONO-AE1-329) can protect against colitis in rats (Nitta *et al* in *Scandinavian Journal of Immunology* 2002, 56(1), 66-75).

Doré *et al* in *The European Journal of Neuroscience* 2005, 22(9), 2199-206 have shown that PGE_2 can protect neurons against amyloid beta peptide toxicity by acting on EP_2 and EP_4 receptors. Furthermore Doré has demonstrated in *Brain Research* 2005, 1066(1-2), 71-77 that an EP_4 receptor agonist (ONO-AE1-329) protects against neurotoxicity in an acute model of excitotoxicity in the brain.

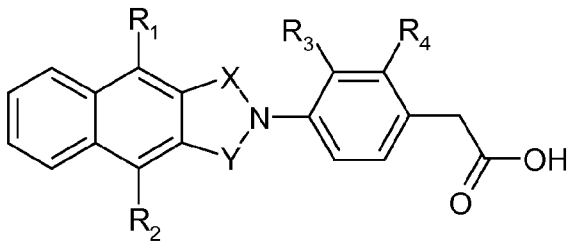
Woodward *et al* in Journal of Lipid Mediators 1993, 6(1-3), 545-53 found intraocular pressure could be lowered using selective prostanoid agonists. Two papers in Investigative Ophthalmology & Visual Science have shown the prostanoid EP_4 receptor is expressed in human lens epithelial cells (Mukhopadhyay *et al* 1999, 40(1), 105-12), and suggest a physiological role for the prostanoid EP_4 receptor in modulation of flow in the trabecular framework of the eye (Hoyng *et al* 1999, 40(11), 2622-6).

Compounds exhibiting EP_4 receptor binding activity and their uses have been described in, for example, WO98/55468, WO00/18744, WO00/03980, WO00/15608, WO00/16760, WO00/21532, WO01010426, EP0855389, EP0985663, WO02/047669, WO02/50031, WO02/50032, WO02/50033, WO02/064564, WO03/103604, WO03/077910, WO03/086371, WO04/037813, WO04/067524, WO04/085430, US04/142969, WO05/021508, WO05/105733, WO05/105732, WO05/080367, WO05/037812, WO05/116010 and WO06/122403.

Derivatives of indoprofen such as [4-(1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]-2-propionic acid, sodium salt have been described by Rufer et. al. in *Eur. J. Med. Chem. – Chimica Therapeutica*, **1978**, 13, 193.

The compounds of the present invention have surprisingly been shown to exhibit advantageous activity in some biological assays.

The present invention provides compounds of formula (I) and/or pharmaceutically acceptable derivatives thereof,



(I)

wherein,

R_1 represents C_{1-4} alkyl or C_{1-4} alkoxy;

R_2 represents C_{1-4} alkyl or C_{1-4} alkenyl;

R_3 represents H, F, Cl, methyl, methoxy or CF_3;

R_4 represents H or F;

X represents CH_2 or C=O; and

Y represents CH_2 or C=O, provided that at least one of X and Y represents C=O and at least one of R_3 and R_4 is H.

In one embodiment of the invention R_1 represents C_{1-4}alkyl. In a further embodiment of the invention R_1 represents propyl. In another embodiment R_1 represents C_{1-4}alkoxy. In a further embodiment R_1 represents ethoxy.

In one embodiment of the invention R_2 represents C_{1-4} alkyl. In a further embodiment of the invention R_2 represents C_2 alkyl. In a yet further embodiment of the invention R_2 represents C_3 alkyl. In another embodiment of the invention R_2 represents C_4 alkyl. In yet another embodiment of the invention R_2 represents methyl, ethyl, n-propyl or 2-methylpropyl.

In one embodiment of the invention R_2 represents C_{1-4} alkenyl. In a further embodiment of the invention R_2 represents ethenyl or 2-methylpropen-1-yl.

In one embodiment of the invention R_3 represents F. In a further embodiment of the invention R_3 represents H.

In one embodiment of the invention X and Y both represent C=O. In a further embodiment of the invention X represents C=O and Y represents CH_2. In a yet further embodiment of the invention X represents CH_2 and Y represents C=O.

In one embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl and R_3 represents F.

In a further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F and X and Y both represent C=O.

In a yet further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents C=O and Y represents CH_2.

In a still further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents CH_2 and Y represents C=O.

In one embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X and Y both represent C=O and R_1 represents ethoxy.

In a further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents C=O, Y represents CH_2 and R_1 represents ethoxy.

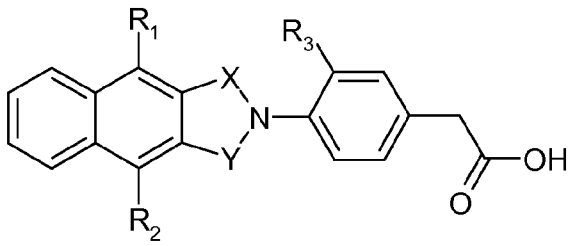
In a yet further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents CH_2, Y represents C=O and R_1 represents ethoxy.

In one embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X and Y both represent C=O and R_1 represents propyl.

In a further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents C=O, Y represents CH_2 and R_1 represents propyl.

In a yet further embodiment of the invention R_2 represents C_2, C_3 or C_4 alkyl, R_3 represents F, X represents CH_2, Y represents C=O and R_1 represents propyl.

In one embodiment of the invention there is provided a subset of compounds of formula (I), of formula (IA) and/or pharmaceutically acceptable derivatives thereof,



(IA)

wherein,

R_1 represents C_{1-4} alkyl or C_{1-4} alkoxy;

R_2 represents C_{1-4} alkyl or C_{1-4} alkenyl;

R_3 represents H or F;

X represents CH_2 or C=O; and

Y represents CH_2 or C=O, provided that at least one of X and Y represents C=O.

In another embodiment of the invention R_1, R_2, R_3, X and Y may have the values ascribed to them in the Examples hereinbelow.

In another embodiment of the invention the compound of formula (I) is selected from:

{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,
{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,
{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,
{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,
{4-[4-(Ethyloxy)-9-methyl-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,
[4-(1,3-Dioxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid,
{4-[9-(Ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,
{4-[4-(Ethyloxy)-1-oxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid, and
[4-(1-Oxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid,
and pharmaceutically acceptable derivatives thereof.

As used herein, the term 'C_{1-4} alkyl' includes straight chain and branched chain alkyl groups containing 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, *iso*-propyl, n-butyl and 2-methylpropyl.

As used herein, the term 'C_{1-4} alkoxy' includes those with straight and branched chains containing 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propxy, *iso*-propoxy, n-butoxy and 2-methylpropoxy.

As used herein, the term 'C_{1-4} alkenyl' includes straight and branched chain alkenyl groups containing 1 to 4 carbon atoms, with one or more double bonds, such as ethenyl, propenyl, n-butenyl and 2-methylpropenyl, which includes 2-methylpropen-1-yl and 2-methylpropen-2-yl.

As used herein, F means fluoro, Cl means chloro and CF_3 means trifluoromethyl.

By pharmaceutically acceptable derivative is meant any pharmaceutically acceptable salt, solvate or ester, or salt or solvate of such ester of the compounds of formula (I), or any other compound which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof.

It will be appreciated that, for pharmaceutical use, the salts referred to above will be the pharmaceutically acceptable salts, but other salts may find use, for example in the preparation of compounds of formula (I) and the pharmaceutically acceptable salts thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.,* 1977, 66, 1-19. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; and cyclic amines. Particular pharmaceutically acceptable organic bases include arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropyl amine, tris(hydroxymethyl)aminomethane, and the like. Salts may also be formed from basic ion exchange resins, for example polyamine resins.

It will be appreciated that the compounds of formula (I) may be produced in vivo by metabolism of a suitable prodrug. Such prodrugs may be for example physiologically acceptable metabolically labile esters of compounds of formula (I). These may be formed by esterification of the carboxylic acid group in the parent compound of formula (I) with, where appropriate, prior protection of any other reactive groups present in the molecule followed by deprotection if required. Examples of such

metabolically labile esters include C_{1-4}alkyl esters e.g. methyl ethyl or t-butyl esters esters, C_{3-6} alkenyl esters e.g. allyl substituted or unsubstituted aminoalkyl esters (e.g. aminoethyl, 2-(N,N- diethylamino) ethyl, or 2-(4-morpholino)ethyl esters or acyloxyalkyl esters such as, acyloxymethyl or 1-acyloxyethyl e.g. pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1- acetoxyethyl,1-(1-methoxy-1-methyl)ethylcarbonyloxyethyl, 1- benzoyloxyethyl, isopropoxycarbonyloxymethyl, 1-isopropoxycarbonyloxyethyl, cyclohexylcarbonyloxymethyl, 1-cyclohexylcarbonyloxyethyl ester, cyclohexyloxycarbonyloxymethyl, 1-cyclohexyloxycarbonyloxyethyl, 1-(4-tetrahydropyranyloxy)carbonyloxyethyl or 1-(4-tetrahydropyranyl)carbonyloxyethyl.

It is to be understood that the present invention encompasses all isomers of the compounds of formula (I) and their pharmaceutically acceptable derivatives, including all geometric, tautomeric and optical forms, and mixtures thereof (e.g. racemic mixtures).

Since the compounds of formula (I) are intended for use in pharmaceutical compositions, it will be understood that they are each provided in substantially pure form, for example at least 50% pure, at least 75% pure and at least 95% pure (% are on a wt/wt basis). Impure preparations of the compounds of formula (I) may be used for preparing the more pure forms used in the pharmaceutical compositions. Although the purity of intermediate compounds of the present invention is less critical, it will be readily understood that the substantially pure form is preferred as for the compounds of formula (I). Whenever possible, the compounds of the present invention are obtained in crystalline form.

When some of the compounds of this invention are allowed to crystallise or are recrystallised from organic solvents, solvent of crystallisation may be present in the crystalline product. This invention includes within its scope such solvates, including solvates of the free acid molecule and solvates of salts derived from the free acid molecule. Similarly, some of the compounds of this invention may be crystallised or recrystallised from solvents containing water. In such cases water of hydration may be formed. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water that may be produced by processes

such as lyophilisation. This invention also includes within its scope anhydrous forms of the compounds of formula (I).

In addition, different crystallisation conditions may lead to the formation of different polymorphic forms of crystalline products. This invention includes within its scope all polymorphic forms of the compounds of formula (I).

The present invention also includes within its scope all isotopically-labelled compounds of formula (I). Such compounds are identical to those recited above except that one or more atoms therein are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of formula (I) and pharmaceutically acceptable derivatives thereof include isotopes of hydrogen, carbon, nitrogen, oxygen and fluorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O and 18F.

Isotopically-labelled compounds of formula (I), for example those into which radioactive isotopes such as 3H, 14C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., 3H, and carbon-14, i.e., 14C, isotopes are particularly preferred for their ease of preparation and detectability. 11C and 18F isotopes are particularly useful in PET (positron emission tomography), and are useful in brain imaging. Further substitution with heavier isotopes such as deuterium, i.e., 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labelled compounds of formula (I) may be prepared by carrying out the synthetic procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent.

The compounds of formula (I) are EP_4 receptor agonists and may therefore be useful in treating EP_4 receptor mediated diseases.

In particular the compounds of formula (I) may be useful in the treatment of pain, for example, chronic articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and juvenile arthritis) including the property of disease

modification and joint structure preservation; musculoskeletal pain; lower back and neck pain; sprains and strains; neuropathic pain; sympathetically maintained pain; myositis; pain associated with cancer and fibromyalgia; pain associated with migraine; pain associated with influenza or other viral infections, such as the common cold; rheumatic fever; pain associated with functional bowel disorders such as non-ulcer dyspepsia, non-cardiac chest pain and irritable bowel syndrome; pain associated with myocardial ischemia; post operative pain; headache; toothache; and dysmenorrhea.

The compounds of formula (I) may be particularly useful in the treatment of neuropathic pain and symptoms associated therewith. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV-related neuropathy; post-herpetic neuralgia; trigeminal neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. Symptoms of neuropathic pain include spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is included pain associated with normally non-painful sensations such as "pins and needles" (paraesthesias and dysesthesias), increased sensitivity to touch (hyperesthesia), painful sensation following innocuous stimulation (dynamic, static or thermal allodynia), increased sensitivity to noxious stimuli (thermal, cold, mechanical hyperalgesia), continuing pain sensation after removal of the stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of formula (I) may also be useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, psoriasis); ophthalmic diseases such as glaucoma, retinitis, retinopathies, uveitis and of acute injury to the eye tissue (e.g. conjunctivitis); lung disorders (e.g. asthma, bronchitis, emphysema, allergic rhinitis, respiratory distress syndrome, pigeon fancier's disease, farmer's lung, COPD); gastrointestinal tract disorders (e.g. aphthous ulcer, Crohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, inflammatory bowel disease, gastrointestinal reflux disease, diarrhoea, constipation); organ transplantation; other conditions with an inflammatory component such as vascular disease, migraine, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma,

myaesthenia gravis, multiple sclerosis, sorcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis, myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of formula (I) may also be useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of formula (I) may also be effective in increasing the latency of HIV infection.

The compounds of formula (I) may also be useful in the treatment of diseases of excessive or unwanted platelet activation such as intermittent claudication, unstable angina, stroke, and acute coronary syndrome (e.g. occlusive vascular diseases).

The compounds of formula (I) may also be useful as a drug with diuretic action, or may be useful to treat overactive bladder syndrome.

The compounds of formula (I) may also be useful in the treatment of impotence or erectile dysfunction.

The compounds of formula (I) may also be useful in the treatment of bone disease characterised by abnormal bone metabolism or resorption such as osteoporosis (especially postmenopausal osteoporosis), hyper-calcemia, hyperparathyroidism, Paget's bone diseases, osteolysis, hypercalcemia of malignancy with or without bone metastases, rheumatoid arthritis, periodontitis, osteoarthritis, ostealgia, osteopenia, calculosis, lithiasis (especially urolithiasis), gout and ankylosing spondylitis, tendinitis and bursitis.

The compounds of formula (I) may also be useful in bone remodelling and/or promoting bone generation and/or promoting fracture healing.

The compounds of formula (I) may also be useful for attenuating the hemodynamic side effects of NSAIDs and COX-2 inhibitors.

The compounds of formula (I) may also be useful in the treatment of cardiovascular diseases such as hypertension or myocardial ischemia; functional or organic venous insufficiency; varicose therapy; haemorrhoids; and shock states associated with a marked drop in arterial pressure (e.g. septic shock).

The compounds of formula (I) may also be useful in the treatment of neurodegenerative diseases such as dementia, particularly degenerative dementia (including senile dementia, Alzheimer's disease, Pick's disease, Huntingdon's chorea, Parkinson's disease and Creutzfeldt-Jakob disease, Amyotrophic lateral sclerosis (ALS), motor neuron disease); vascular dementia (including multi-infarct dementia); as well as dementia associated with intracranial space occupying lesions; trauma; infections and related conditions (including HIV infection); metabolism; toxins; anoxia and vitamin deficiency; and mild cognitive impairment associated with ageing, particularly Age Associated Memory Impairment.

The compounds of formula (I) may also be useful in the treatment of neurological disorders and may be useful as neuroprotecting agents. The compounds of the invention may also be useful in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

The compounds of formula (I) may also be useful in the treatment of complications of Type 1 diabetes (e.g. diabetic microangiopathy, diabetic retinopathy, diabetic nephropathy, macular degeneration, glaucoma), nephrotic syndrome, aplastic anaemia, uveitis, Kawasaki disease and sarcoidosis.

The compounds of formula (I) may also be useful in the treatment of a kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), a liver dysfunction (hepatitis, cirrhosis) and gastrointestinal dysfunction (diarrhoea).

It is to be understood that as used herein any reference to treatment includes both treatment of established symptoms and prophylactic treatment.

In a further embodiment the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

In a yet further embodiment of the invention, there is provided a compound of formula (I) or a pharmaceutically acceptable derivative thereof for use in the treatment of a condition which is mediated by the action, or loss of action, of PGE_2 at EP_4 receptors.

In a still further embodiment of the invention, there is provided a method of treating a human or animal subject suffering from a condition which is mediated by the action, or by loss of action, of PGE_2 at EP_4 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In another embodiment of the invention there is provided a method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological or bone disease, a neurodegenerative disease or a kidney dysfunction, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof.

In one embodiment of the invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_4 receptors.

In a further embodiment of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or kidney disorder.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such

compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

Thus, in another aspect of the invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof adapted for use in human or veterinary medicine.

While it is possible for the compounds of formula (I) or a pharmaceutically acceptable derivative thereof to be administered as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The formulations of the present invention comprise the compounds of formula (I) or a pharmaceutically acceptable derivative thereof together with one or more acceptable carriers or diluents therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Thus, in one embodiment the invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier or diluent therefor.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy (see for example methods disclosed in 'Remington – The Science and Practice of Pharmacy', 21st Edition, Lippincott, Williams & Wilkins, USA, 2005 and references therein). All methods include the step of bringing into association the compound of formula (I) or a pharmaceutically acceptable derivative thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis

such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

The compounds of formula (I) may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of formula (I) may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of formula (I) may be used in combination with other therapeutic agents, for example COX-2 inhibitors, such as celecoxib, rofecoxib, valdecoxib or parecoxib; 5-lipoxygenase inhibitors; analgesics such as paracetamol; NSAID's, such as diclofenac, indomethacin, nabumetone, naproxen or ibuprofen; leukotriene receptor antagonists; DMARD's such as methotrexate; sodium channel blockers, such as lamotrigine; N-type calcium channel antagonists; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin, pregabalin and related compounds; tricyclic antidepressants such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors such as venlafaxine; opioid analgesics; local anaesthetics; $5HT_1$ agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP_1 receptor ligands; EP_2 receptor ligands; EP_3 receptor ligands; EP_1 antagonists; EP_2 antagonists and EP_3 antagonists; cannabanoid receptor agonists; VR1 antagonists. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further embodiment, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together

with a further therapeutic agent or agents. In one embodiment of the invention there is provided a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof and paracetamol.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. In particular there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof, paracetamol and a pharmaceutically acceptable carrier or diluent therefore. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

In one embodiment of the invention there is provided a method of treating a human or animal subject suffering from a condition which is mediated by the action, or by loss of action, of PGE_2 at EP_4 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof and paracetamol.

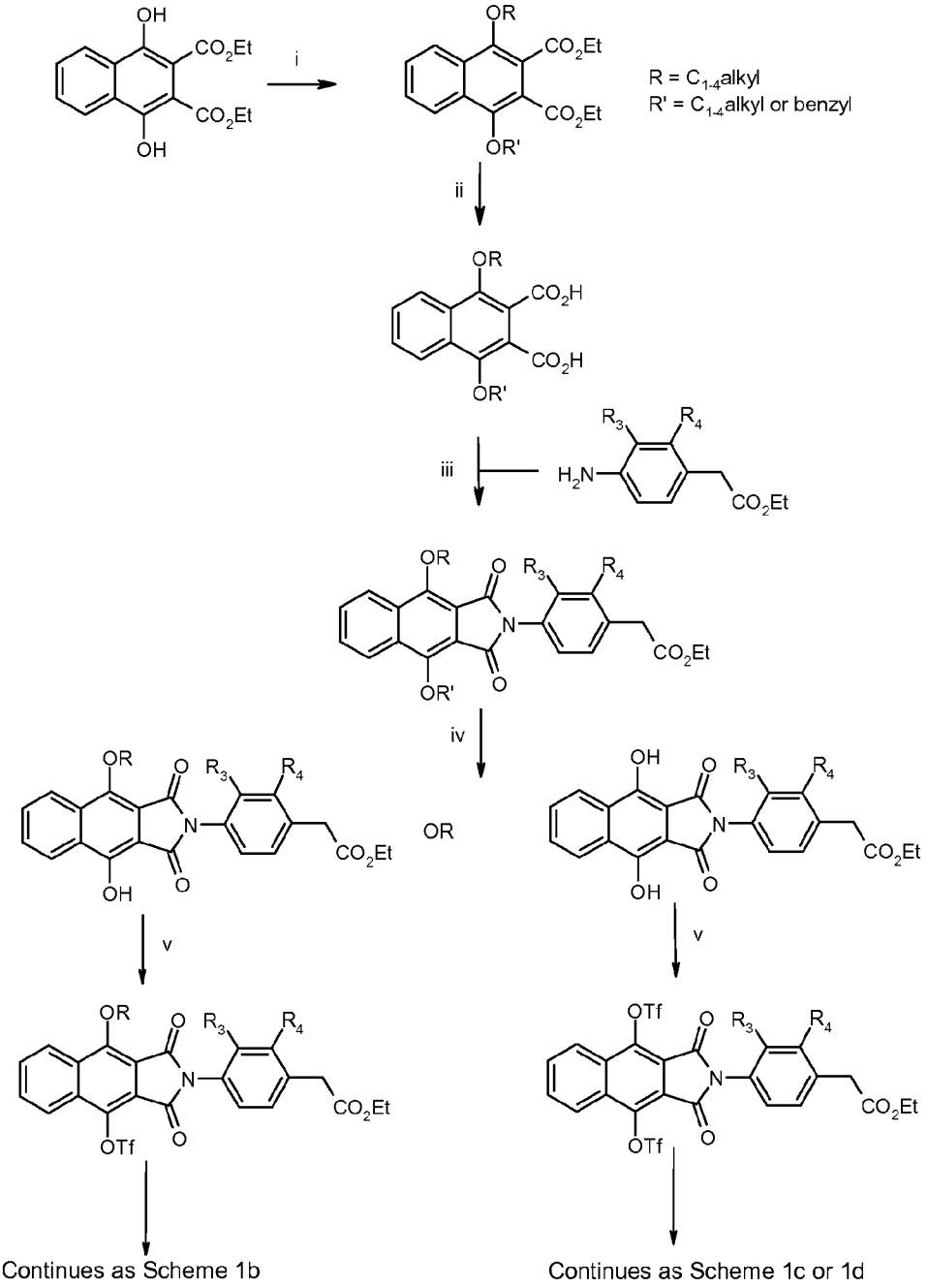
A proposed daily dosage of compounds of formula (I) or their pharmaceutically acceptable salts for the treatment of man is from 0.001 to 30 mg/kg body weight per day and more particularly 0.1 to 3 mg/kg body weight per day, calculated as the free acid, which may be administered as a single or divided dose, for example one to four times per day. The dose range for adult human beings is generally from 0.1 to 1000 mg/day, such as from 10 to 800 mg/day, preferably 10 to 200 mg/day, calculated as the free acid.

A suitable daily dosage of paracetamol is up to 4000 mg per day. Suitable unit doses include 200, 400, 500 and 1000 mg, one, two, three or four times per day.

The precise amount of the compounds of formula (I) administered to a host, particularly a human patient, will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors including the age and sex of the patient, the precise condition being treated and its severity, the route of administration, and any possible combination therapy that may be being undertaken.

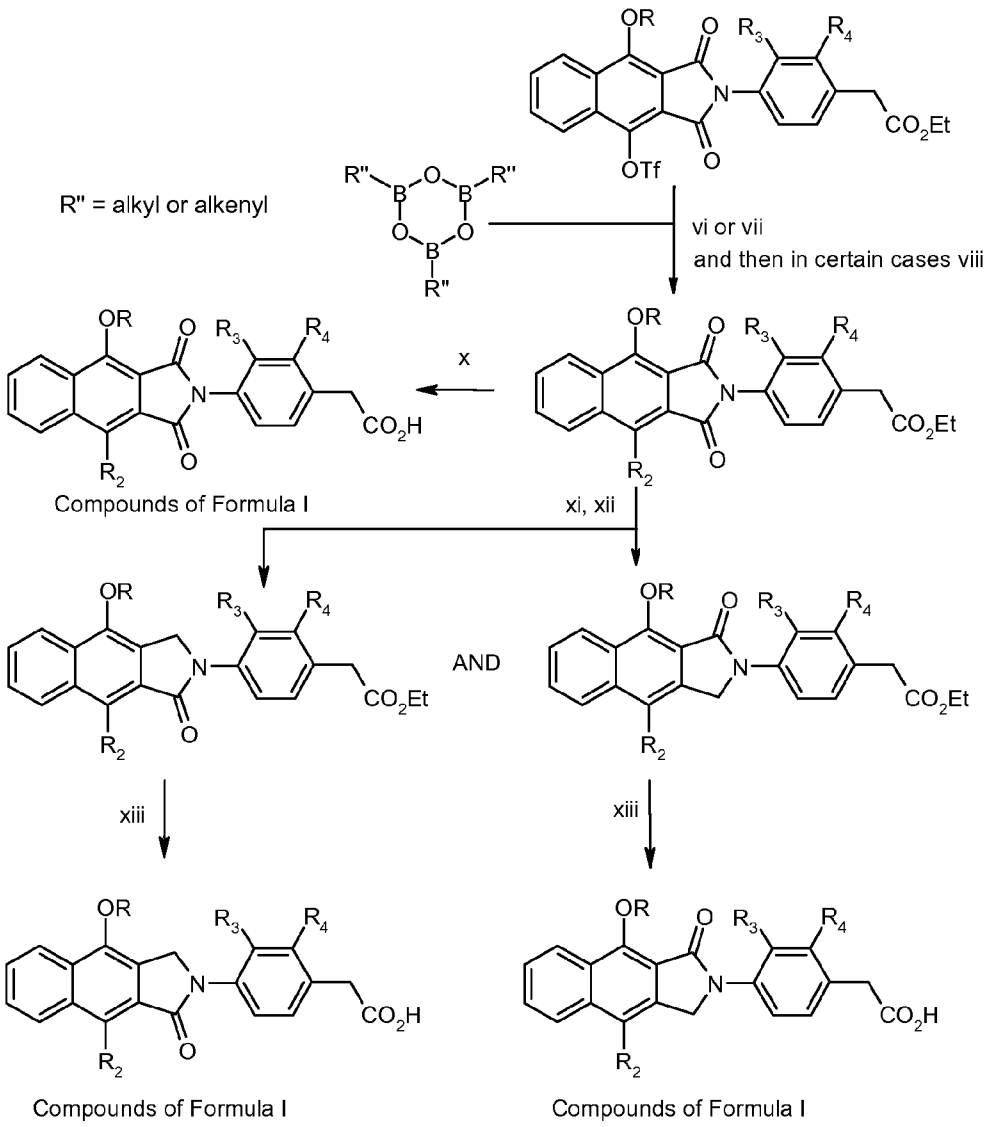
The present invention also provides a process for preparing the compounds of formula (I) and pharmaceutically acceptable derivatives thereof.

Compounds of formula (I) may be prepared using methods well known to the skilled person, using starting materials that are readily available or which can be synthesised using well established methods and techniques. For example, compounds of formula (I) may be made according to scheme 1 which for convenience has been broken down into schemes 1a-1c. Compounds of formula (I) in which R_1 is C_{1-4}alkoxy may be made according to schemes 1a and 1b. Compounds of formula (I) in which R_1 is C_{1-4}alkyl may be made according to schemes 1a and 1c.



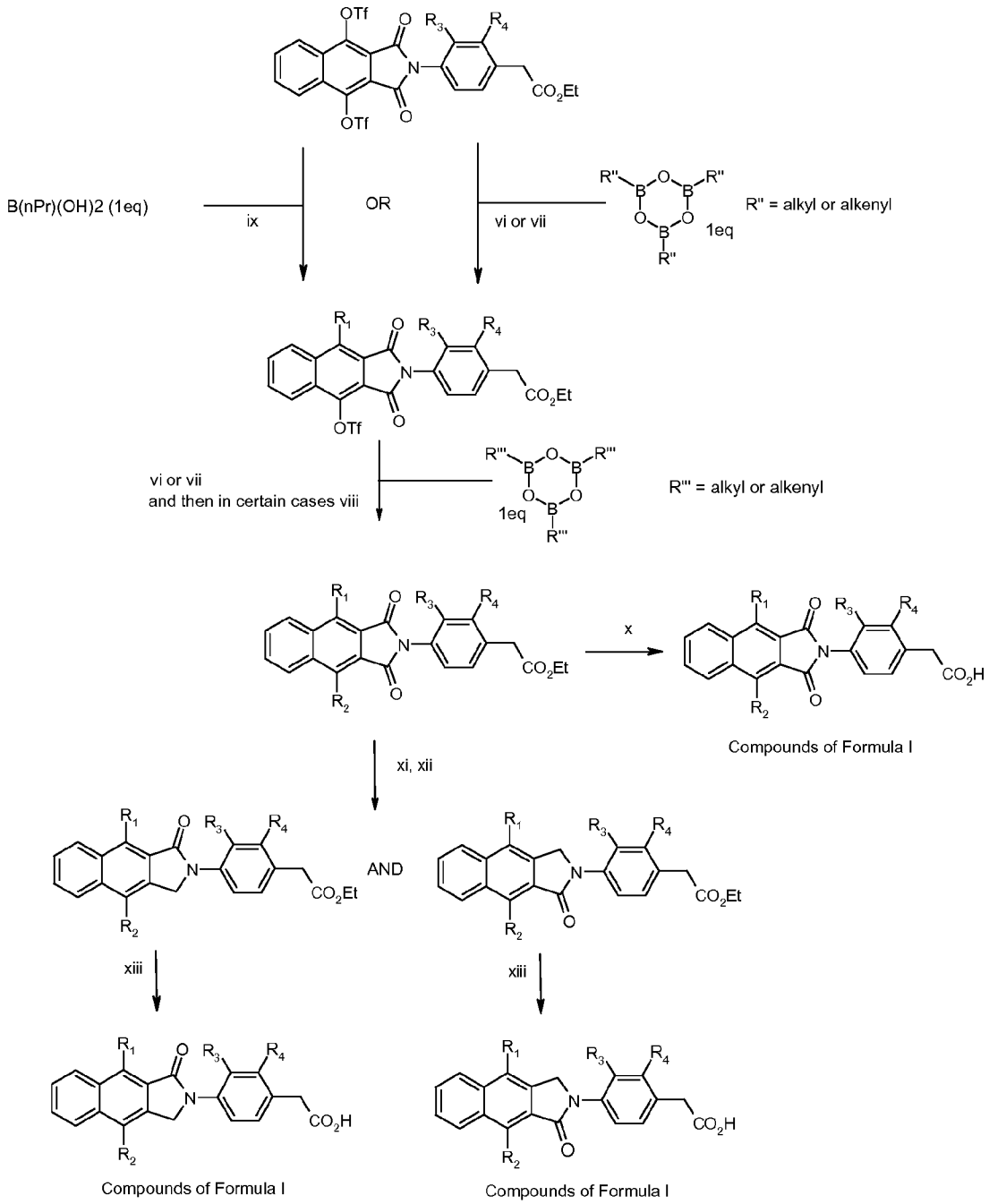
i) RBr, K_2CO_3, CH_3COCH_3, then R'Br, K_2CO_3, CH_3COCH_3; ii) NaOH, EtOH; iii) AcOH; iv) H_2, 10% Pd/C, EtOH or EtOH/EtOAc; v) Tf_2O, CH_2Cl_2, Pyridine

Scheme 1a



vi) $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O; vii) $Pd(PPh_3)_4$, K_2CO_3, Dioxane, H_2O; viii) H_2, 10%Pd/C, EtOAc; xi) $NaBH_4$, EtOH, THF; xii) TFA then Et_3SiH; xiii) NaOH, EtOH.

Scheme 1b



vi) $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O; vii) $Pd(PPh_3)_4$, K_2CO_3, Dioxane, H_2O; viii) H_2, 10%Pd/C, EtOAc; ix) $PdCl_2(dppf)$, Ag_2O, K_2CO_3, THF; x) AcOH, HCl; xi) $NaBH_4$, EtOH, THF; xii) TFA then Et_3SiH; xiii) NaOH, EtOH.

Scheme 1c

In schemes 1b and 1c where it is stated that step viii can be used in certain cases, it is meant that step viii can be used for the production of certain intermediates which will be clear to the skilled person.

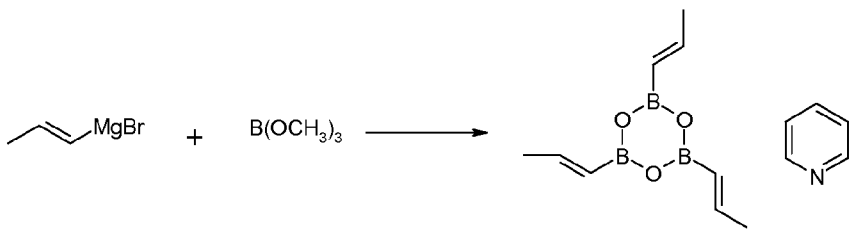
The following Descriptions and Examples illustrate the preparation of compounds of formula (I). Descriptions refer to intermediate compounds and Examples refer to compounds of formula (I). The starting material for the preparation of intermediates may not necessarily have been prepared from the batch referred to. The intermediates for the preparation of the examples may not necessarily have been prepared from the batch referred to.

Abbreviations

DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOH	Ethanol
EtOAc	Ethyl acetate
HCl	Hydrochloric acid
LC/MS	Liquid chromatography/Mass spectroscopy
MDAP	Mass Directed Auto Preparation
NaOH	Sodium hydroxide
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

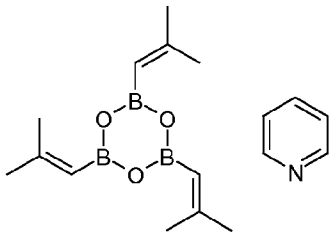
Description 1

Pyridine - tri-(1E)-1-propen-1-ylboroxin



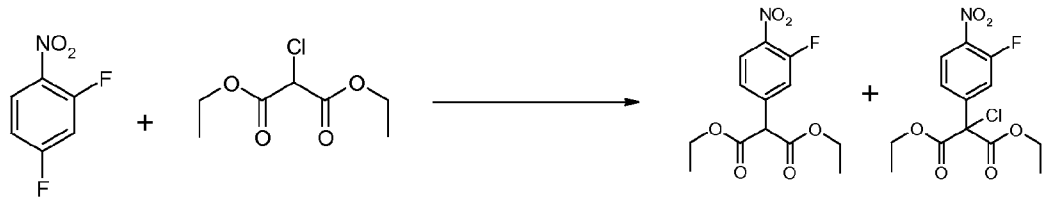
Trimethylborate (5.1ml, 45mmol) was cooled to -78°C in dry tetrahydrofuran (50ml). 1-Propenylmagnesium bromide (50ml, 25mmol) was added dropwise over 1.5 hours. Stirred for 1 hour at -78°C. 1M HCl was added dropwise over 10 minutes and allowed to warm to room temperature. Brine (50ml) was added and transferred to a separating funnel. Aqueous was extracted with diethyl ether (3x 100ml). Combined organics were washed with water (50ml), brine (50ml) and dried over magnesium sulphate. Diethyl ether solution was evaporated to ~25ml and treated with pyridine (5ml). Stirred overnight at room temperature, then solvent evaporated to give the title compound as a yellow oil (2.4g). NMR indicates ~3:1 ratio of pyridine to boroxin.

The following compound was synthesised in a similar manner to pyridine - tri-(1*E*)-1-propen-1-ylboroxin (D1) using the appropriate starting materials.

Description		**Name**	
2		*Pyridine - tris(2-methyl-1-propen-1-yl)boroxin*	NMR indicates ~1.6:1 ratio of pyridine to boroxine

Description 3

Diethyl (3-fluoro-4-nitrophenyl)propanedioate and Diethyl chloro(3-fluoro-4-nitrophenyl)propanedioate



2,4-Difluoronitrobenzene (45.6g, 287mmol) and diethylchloromalonate (55.7g, 287mmol) dissolved in dry DMF (300ml) was cooled in an ice bath. Crushed sodium hydroxide (23g) was added portionwise over 20 minutes. Reaction mixture was stirred

at room temperature overnight. Reaction again cooled in an ice bath and acidified with 2N HCl (~400ml). Extracted with ethyl acetate (2x400ml, 1x200ml), organics washed with water (400ml), brine (400ml) and dried over $MgSO_4$. Evaporated to give an orange oil (~89g). Material was purified by flash chromatography, and loaded onto 1.5Kg Si cartridge eluting 0-20% ethyl acetate in hexane over 10CV on the companion XL. Fractions were evaporated to give the title compounds as their single components and as a mixture.

Diethyl chloro(3-fluoro-4-nitrophenyl)propanedioate as a yellow oil (9.1g, 27.3mmol).

LC/MS: Rt=3.18, no mass ion.

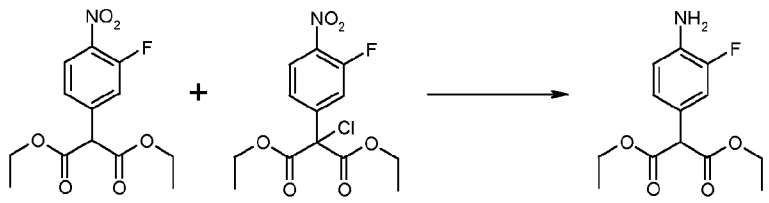
Diethyl (3-fluoro-4-nitrophenyl)propanedioate as a yellow oil (24.7g, 82.6mmol).

LC/MS: Rt=2.96, $[MH]^+$300.

Diethyl chloro(3-fluoro-4-nitrophenyl)propanedioate and diethyl (3-fluoro-4-nitrophenyl)propanedioate as ~1:1 mixture (1.7g, 5.5mmol).

Description 4

Diethyl (4-amino-3-fluorophenyl)propanedioate



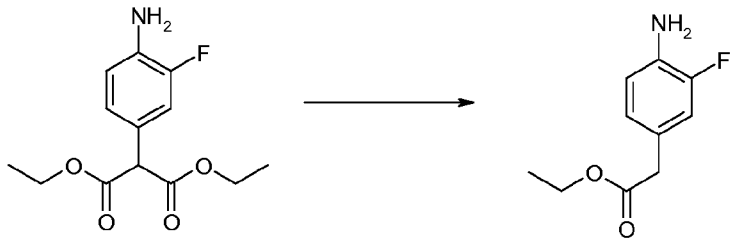
The mixture of starting materials diethyl (3-fluoro-4-nitrophenyl)propanedioate and diethyl chloro(3-fluoro-4-nitrophenyl)propanedioate (D3) (1.7g, ~5.7mmol) suspended in ethanol was treated with 5-10ml ethyl acetate so in solution. This was treated with 10% Pd/C (wet paste) (170mg) under argon and then ammonium formate (1.8g, 5eq) added. Stirred for 1 hour at reflux under argon. Reaction complete. Cooled

to room temperature and Pd removed by filtration through celite, under argon. Evaporated to a brown oil ~1.7g. Purified by flash chromatography, 40+M Si cartridge, eluting 5-40% ethyl acetate in hexane over 10CV on Biotage SP4™. Fractions evaporated to give the title compound as a yellow oil (722mg, 2.7mmol).

LC/MS: Rt=2.65, $[MH]^+$270

Description 5

Ethyl (4-amino-3-fluorophenyl)acetate

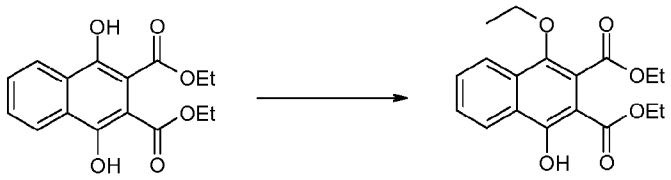


Diethyl (4-amino-3-fluorophenyl)propanedioate (D4) (11.8g, 44.1mmol) was dissolved in ethanol (80ml) and treated with sodium hydroxide (2.6g, 1.5eq) dissolved in 18ml of water to give a pink solution. This was heated to 90°C for 2 hours until complete, and then cooled to room temperature. Solvent evaporated and acidified with 2N HCl. Extracted with ethyl acetate (3x 100ml). Organics washed with brine and dried over $MgSO_4$. Evaporated to give the title compound as a yellow oil which crystallised slowly on standing. (6.6g, 33.5mmol).

LC/MS: Rt=2.28, $[MH]^+$198.

Description 6

Diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate

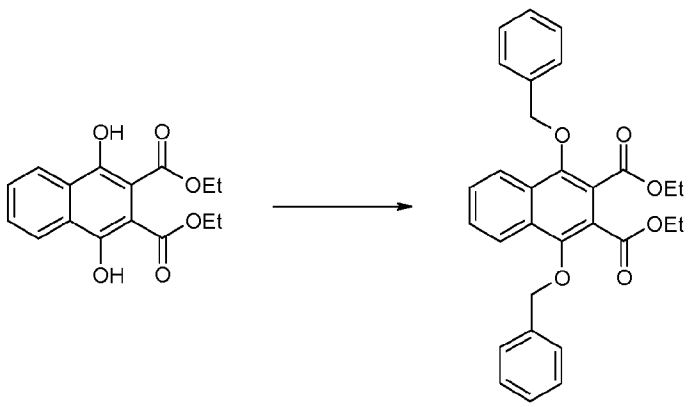


Diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (5.0g,16.4mmol) was dissolved in acetone (100ml) and treated with potassium carbonate (2.4g, 17.3mmol). Stirred for 30 minutes at room temperature. Warmed to 60°C and bromoethane (1.3ml, 17.3mmol) was added dropwise. Continued stirring at 60°C overnight. Cooled to room temperature and filtered. Evaporated to a brown oil which was partitioned between ethyl acetate and brine. Aqueous was extracted with ethyl acetate x3. Organics were washed with water and dried over magnesium sulphate. Evaporated to a brown oil. Material was divided onto 3x 40+M silica cartridges and purified by flash chromatography using the Biotage SP4™, eluting 0-10% ethyl acetate in hexane. Fractions evaporated to give the title compound as a yellow oil which crystallised on standing (3.9g, 11.7mmol).

LC/MS: Rt=3.71, $[MH]^-$ 331

Description 7

Diethyl 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate



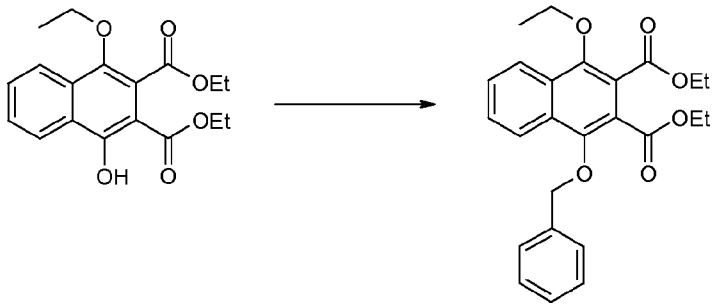
Diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (5g, 16.4mmol) was dissolved in acetone (100ml), treated with potassium carbonate (5.05g, 41.1mmol) and stirred for 10 minutes. Benzyl bromide (4.9ml, 41.1mmol) was added and heated to 60°C overnight. Cooled to room temperature and stood for 24 hours. Inorganics removed by filtration and solvent evaporated to solid. Partitioned between ethyl acetate (100ml) and brine (100ml). Aqueous extracted with ethyl acetate (100ml). Organics washed with water (100ml) and dried over magnesium sulphate. Evaporated to give a cream

solid (~9.5g). Triturated with hexane to give the title compound as a cream solid (6.78g, 14.01mmol).

LC/MS: Rt=4.10, $[MH]^+$ 485

Description 8

Diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate

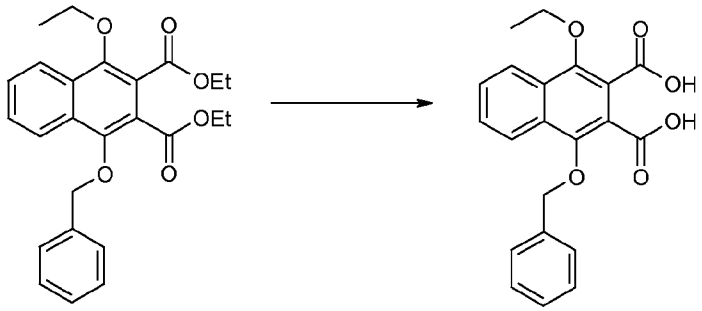


Diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate (D6) (6.5g, 19.6mmol) was dissolved in acetone (150ml) and treated with potassium carbonate (3.6g, 29.4mmol). Stirred for 10 minutes at room temperature. Benzyl bromide (3.5ml. 29.4mmol) was added and stirred under argon at 60°C for 2.5 hours. Cooled to room temperature and stood overnight at room temperature under argon. Solvent evaporated and partitioned between ethyl acetate and brine. Aqueous was extracted with ethyl acetate x2 and organics washed with water. Dried over magnesium sulphate and evaporated to give a yellow oil (9.6g). Material was combined with a second batch (7.0g) and purified by flash chromatography using a 75+M silica cartridge, eluting 0-15% ethyl acetate in hexane over 16CV on the Biotage Flash 75™. Evaporated to give the title compound as a yellow oil (13.85g, 32.8mmol).

LC/MS: Rt=3.74, $[MH]^+$423

Description 9

1-(Ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid

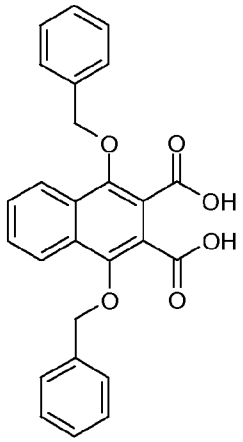


Diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate (D8) (13.9g, 32.8mmol) was dissolved in ethanol (150ml) and treated with 2N sodium hydroxide (50ml). Heated to 90°C for 5 hours, then cooled to room temperature and solvent evaporated to a pink solid. Water was added and acidified with 2N HCl in an ice bath to pH1. Extracted with ethyl acetate (x3) and combined organics washed with water brine and dried over magnesium sulphate. Evaporated to give the title compound as a yellow oil which crystallised on standing, (11.3g, 30.7mmol).

LC/MS: Rt=2.73, $[MH]^-$365

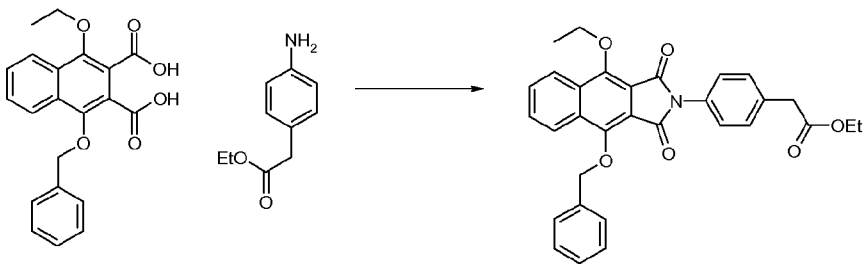
The following compound was prepared in a similar manner to 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (D9) using the appropriate starting materials. Heated for 2.5 hours. Prepcipitate on acidifying was filtered washed with water and dried in a vacuum oven overnight.

5

Description		Name	LC/MS
10		*1,4-Bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid*	Rt=3.15 $[MH]^+$ 429

10 **Description 11**

Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



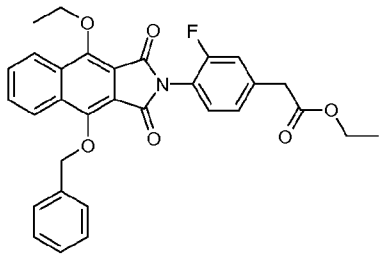
15

1-(Ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (D9) (2.5g, 6.8mmol) was dissolved in acetic acid (50ml) and treated with ethyl-4-aminophenylacetate (2.4g, 13.6mmol). Reaction mixture was heated at 120°C for 2

hours until completion. Cooled to room temperature and water was added and extracted with ethyl acetate. Organics washed with water and brine, then dried over magnesium sulphate. Evaporated to give an oil which crystallised on standing. This was triturated with cold diethyl ether to give the title compound as a white solid (2.2g, 4.2mmol).

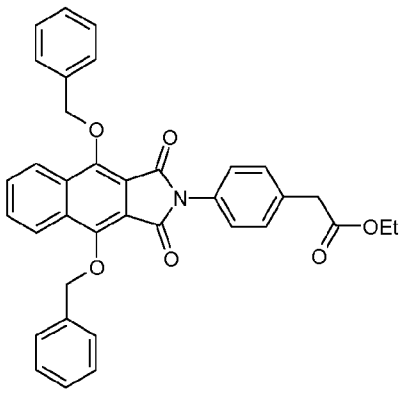
LC/MS: Rt=3.88, $[MH]^+$510

The following compound was prepared in a similar manner to ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D11) using the appropriate starting materials. Crude material was purified by flash chromatography using a 40+M silica cartridge, eluting 0-35% ethyl acetate over 10CV on Biotage SP4™.

Description		Name	LC/MS
12		*Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.89 $[MH]^+$528

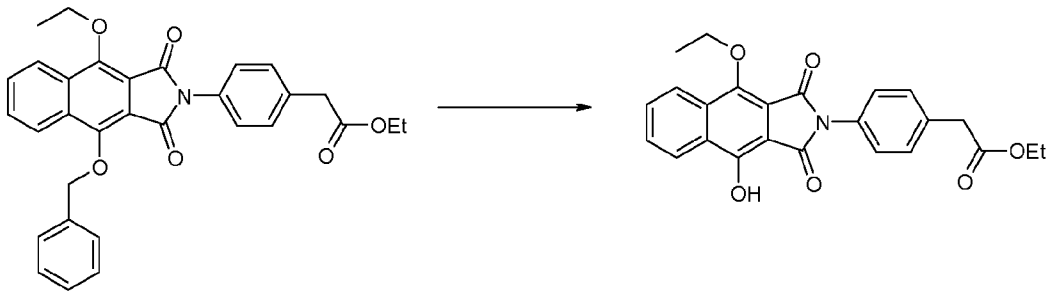
The following compound was prepared in a similar manner to ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D11) using the appropriate staring materials . Solid was precipitated on addition of water, which was filtered, washed with water and triturated with diethyl ether.

Description		Name	LC/MS

13		*Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.97 $[MH]^+$ 572

Description 14

Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate

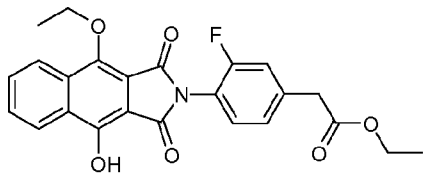


Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D11) (2.1g, 4.2mmol) was suspended in ethanol (100ml) and 10% Pd/C (wet paste) (215mg) was added under argon. Reaction mixture was stirred at room temperature and atmospheric pressure under an atmosphere of hydrogen for 4-5 hours. The catalyst was removed by filtration through celite under argon washing through with DCM. Solvent evaporated to give the title compound as a yellow solid, (1.8g, 4.3mmol).

LC/MS: Rt=3.53, $[MH]^+$420

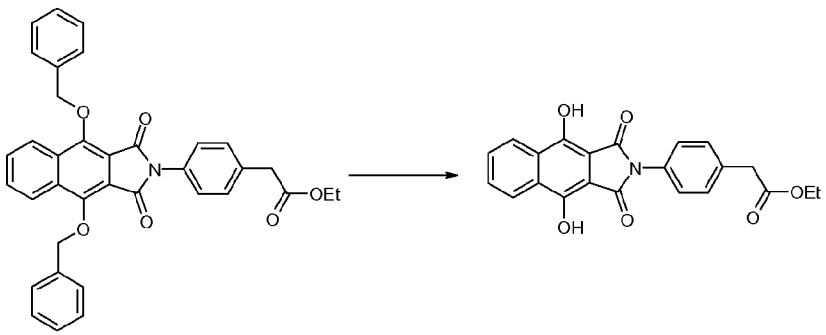
The following compound was prepared in a similar manner to ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D14) using the appropriate staring materials.

5

Description		Name	LC/MS
15		*Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.62 $[MH]^+$438

10 **Description 16**

Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



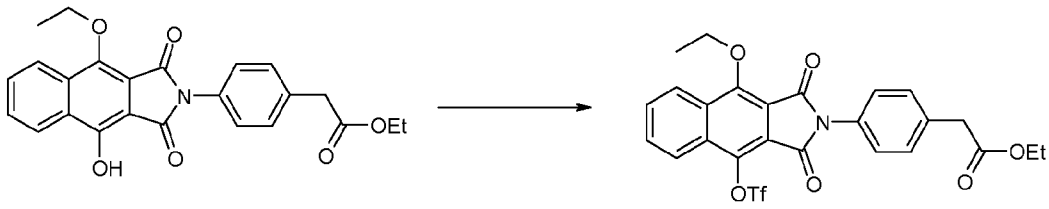
15 Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D13) (3.3g, 5.7mmol) was suspended in ethanol (100ml). 20ml of ethyl acetate was added. 10% Pd/C (wet paste) (530mg) was added under argon. Reaction was stirred under a hydrogen atmosphere for 2 hours. Cataylst was removed

by filtration under argon, washing with DCM. Solution was evaporated to give the title compound as a yellow solid (2.1g, 5.4mmol).

LC/MS: Rt=3.18, $[MH]^+$ 392

Description 17

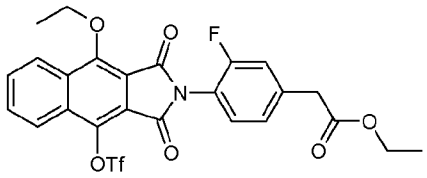
Ethyl [4-(4-(ethyloxy)-1,3-dioxo-9-{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D14) 1.8g, 4.3mmol) was dissolved in dichloromethane (60ml) and treated with pyridine (0.35ml, 4.3mmol) and stirred for 10 minutes at room temperature, followed by triflic anhydride (0.71ml, 4.3mmol) dropwise. Stirring continued for 1 hour at room temperature under argon. Reaction mixture was evaporated to a solid. Redissolved in DCM and washed with 1M HCl, and water and then dried over magnesium sulphate. Evaporated to give the title compound as a cream solid, (2.2g, 4.1mmol).

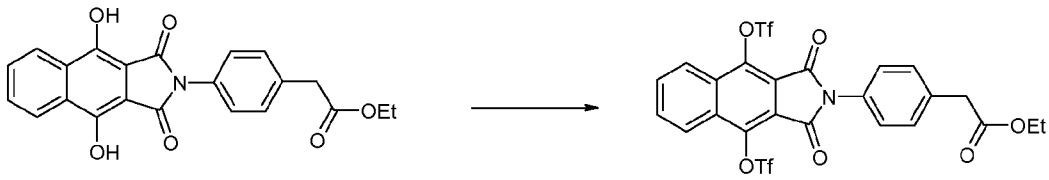
LC/MS: Rt=3.88 $[MH]^+$552

The following compound was prepared in a similar manner to ethyl [4-(4-(ethyloxy)-1,3-dioxo-9-{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)phenyl]acetate (D17) using the appropriate staring materials.

Description		Name	LC/MS
18		*Ethyl [4-(4-(ethyloxy)-1,3-dioxo-9-{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-fluorophenyl]acetate*	Rt=3.78 $[MH]^+$570

Description 19

Ethyl [4-(1,3-dioxo-4,9-bis{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate

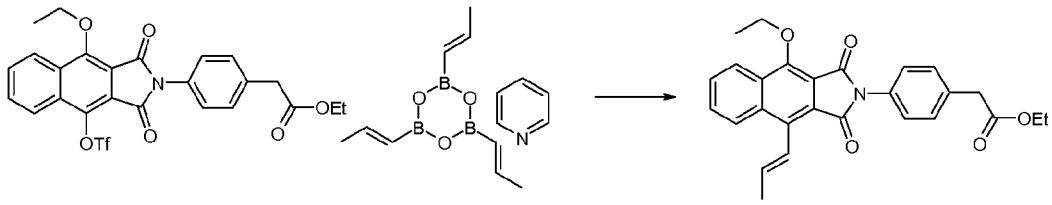


Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (D16) (2.1g, 5.4mmol) was dissolved in DCM (150ml) and treated with pyridine (0.87ml, 10.8mmol). Triflic anhydride (1.78ml, 10.8mmol) was added at 0°C. Stirred at room temperature under argon for 2 hours. A further 0.5 equivilents of both pyridine and triflic anhydride were added. On completion evaporated to soild. Redissolved in DCM and washed with 1M HCl (100ml). Aqueous extracted with DCM (100ml). combined DCM extracts were washed with water and dried over magnesium sulphate. Evaporated to give the title compound as a beige solid (3.4g, 5.2mmol)

LC/MS: Rt=3.69, $[MH]^+$ 656

Description 20

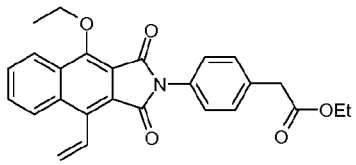
Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(1E)-1-propen-1-yl]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate

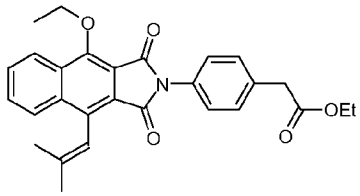
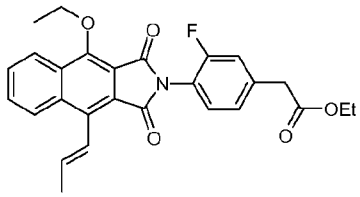
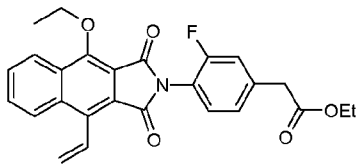
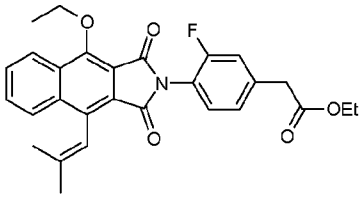


Ethyl [4-(4-(ethyloxy)-1,3-dioxo-9-{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)phenyl]acetate (D17) (500mg, 0.9mmol) was dissolved in DME (20ml) and $Pd(PPh_3)_4$ (52mg, 0.05mmol) was added and stirred for 20 minutes under argon. Potassium carbonate (124mg, 0.9mmol), water (5ml), and pyridine - tri-(1*E*)-1-propen-1-ylboroxin (D1) (595mg, 1.4mmol) were then added and heated at 90°C for 1 hour. Reaction mixture was cooled to room temperature and water added. This was extracted with diethyl ether (x3). Combined organics were washed with sodium hydrogen carbonate solution, water, 2N HCl water, brine and dried over magnesium sulphate. Evaporated to give a yellow oil. Crude material was purified by flash chromatography, using 40+S silica cartridge, eluting 0-25% ethyl acetate in hexane over 10CV on Biotage SP4™. Fractions evaporated to give the title compound as a yellow oil which crystallised on standing (407mg, 0.9mmol). NMR and LCMS indicate a mixture of cis and trans products.

LC/MS Rt=3.77, 3.85 $[MH]^+$ 444

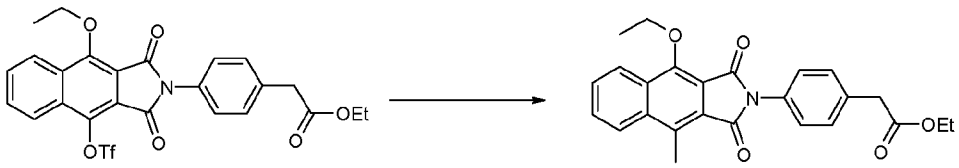
The following compounds were prepared in a similar manner to ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(1*E*)-1-propen-1-yl]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D20) using the appropriate starting materials.

Description		Name	LC/MS
21		*Ethyl {4-[4-ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.82 $[MH]^+$430

22		*Ethyl {4-[4-(ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.90 $[MH]^+$458
23		*Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(1E)-1-propen-1-yl]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.87,3.95 $[MH]^+$462
24		*Ethyl {4-[4-ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.84 $[MH]^+$448
25		*Ethyl {4-[4-(ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.99 $[MH]^+$476

Description 26

Ethyl {4-[4-(ethyloxy)-9-methyl-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate

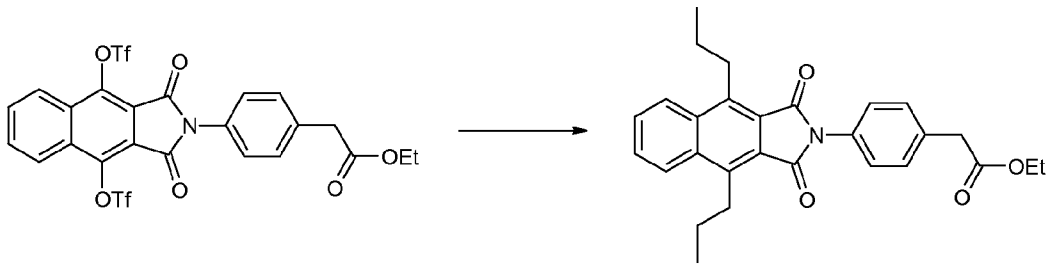


Ethyl [4-(4-(ethyloxy)-1,3-dioxo-9-{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)phenyl]acetate (D17) (215mg, 0.4mmol) was dissolved in 10% aqueous dioxane (10ml) and treated with tetrakis(triphenylphosphine)palladium (45mg, 0.04mmol), potassium carbonate (161mg, 1.17mmol) and trimethylboroxine (0.06ml, 0.39mmol). Heated at 100°C for approximately 2.5hours. Reaction was cooled to room temperature and stood overnight. Filtered through celite, washing with THF. Evaporated to a brown oil which was purified by flash chromatography eluting with 0-35% ethyl acetate in hexane over 10CV. Fractions were evaporated to give the title compound as a yellow solid (63mg, 0.15mmol).

LC/MS: Rt=3.63, $[MH]^+$ 418

Description 27

Ethyl [4-(1,3-dioxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



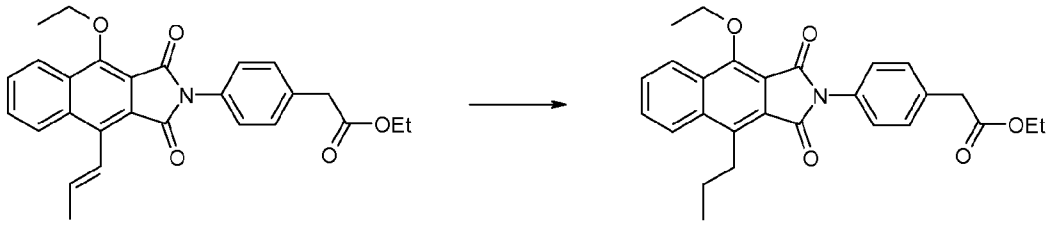
Ethyl [4-(1,3-dioxo-4,9-bis{[(trifluoromethyl)sulfonyl]oxy}-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate (D19) (150mg, 0.23mmol) was added to a mixture of n-propyl boronic acid (45mg, 0.51mmol), $PdCl_2$(dppf) (18mg, 0.02mmol), silver (I) oxide (133mg, 0.57mmol) and potassium carbonate (95mg, 0.69mmol) suspended in THF (5ml). Mixture was heated at 80°C overnight. A further 2.5eq of silver oxide and 3eq of potassium carbonate and 0.1eq of $PdCl_2$(dppf) was added and continued heating for a further 7 hours. Reaction cooled to room temperature and

portioned between ethyl acetate (10ml) and water (10ml). Aqueous was extracted with ethyl acetate (2x10ml). Combined organics dried over magnesium sulphate and evaporated to a yellow oil. Crude material was purified by flash chromatography, eluting 0-20% ethyl acetate in hexane. Fractions evaporated to give the title compound as a white solid (18mg, 0.04mmol).

LC/MS: Rt=4.20, $[MH]^+$ 444.

Description 28

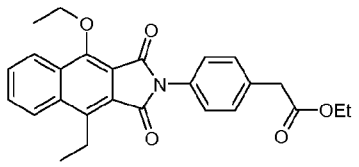
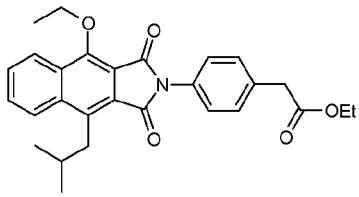
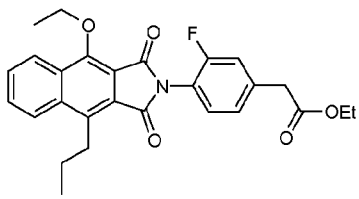
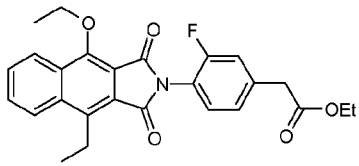
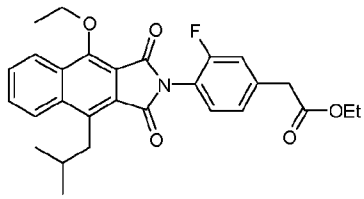
Ethyl {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate



Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(1*E*)-1-propen-1-yl]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (D20) (466mg, 1.07mmol) was dissolved in ethyl acetate(40ml) and 10% Pd/C (wet paste) (50mg) was added under argon. Reaction mixture was stirred under a hydrogen atmosphere at room temperature and atmospheric pressure for 5 hours. Catalyst was removed by filtration through celite under argon, washing through well with DCM. Solvent evaporated to give the title compound as a yellow solid (445mg, 1mmol).

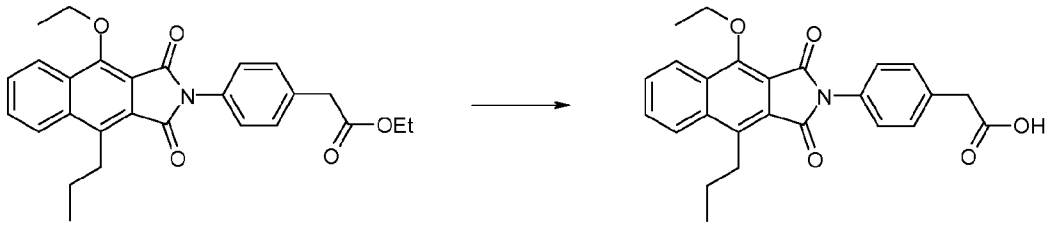
LC/MS: Rt=3.86, $[MH]^+$ 446.

The following compounds were prepared in a similar manner to ethyl {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D28) using the appropriate starting materials.

Description		Name	LC/MS
29		*Ethyl {4-[4-ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.88 $[MH]^+$432
30		*Ethyl {4-[4-(ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=4.07 $[MH]^+$460
31		*Ethyl {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.97 $[MH]^+$464
32		*Ethyl {4-[4-ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.76 $[MH]^+$450
33		*Ethyl {4-[4-(ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=4.09 $[MH]^+$478

Example 1

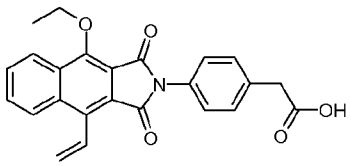
{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid

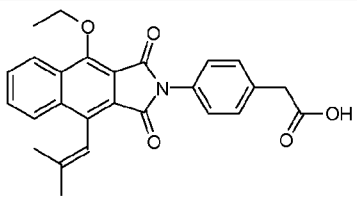
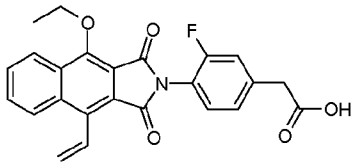
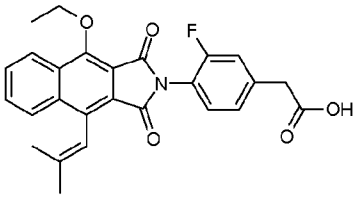
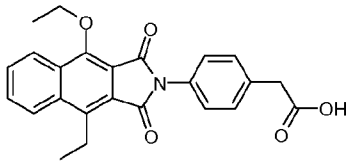
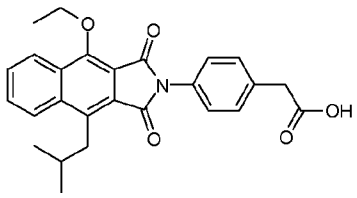
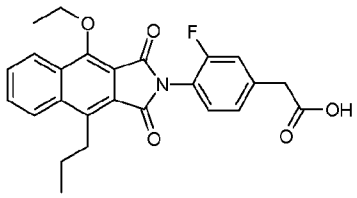


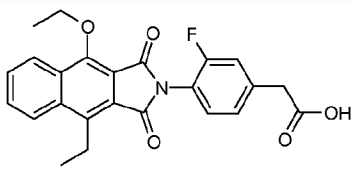
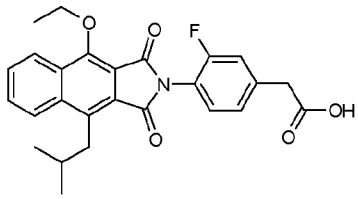
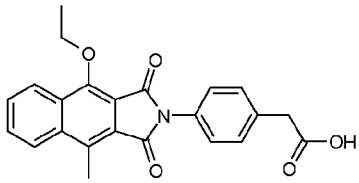
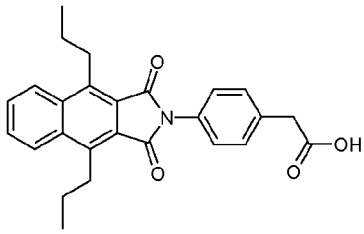
Ethyl {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D28) (75mg, 0.17mmol) was suspended in glacial acetic acid (5ml) and 2N HCl (5ml). Heated to 90°C for 1 hour. Cooled to room temperature and water added. Precipitate was filtered, washed with water, collected and dried in a vacuum oven. White solid was purified by MDAP and dried to give the title compound as a white solid (50mg, 0.12mmol).

LC/MS: Rt=3.52, $[MH]^+$418

The following compounds were prepared in a similar manner to {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetic acid (E1) using the appropriate staring materials.

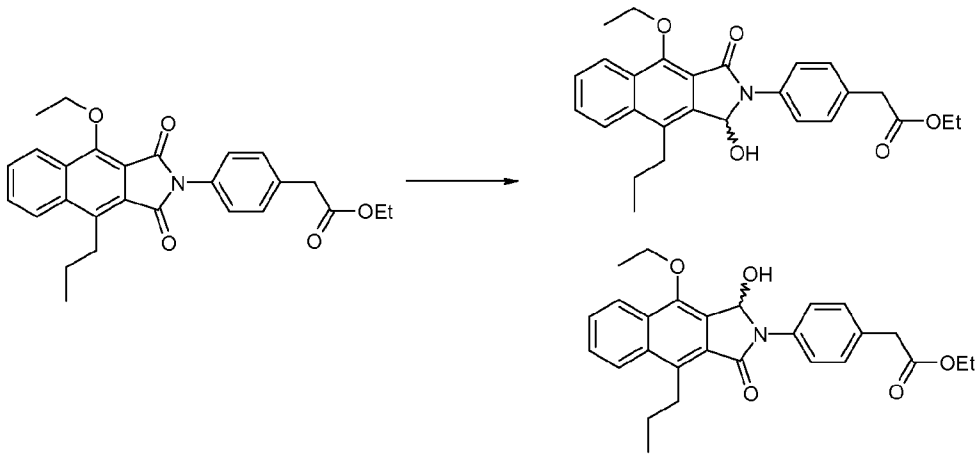
		Name	LC/MS
Example 2		*{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.30 $[MH]^+$402

Example 3		*{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.50 $[MH]^+$430
Example 4		*{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.35 $[MH]^+$420
Example 5		*{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.45 $[MH]^+$448
Example 6		*{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.35 $[MH]^+$404
Example 7		*{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.60 $[MH]^+$432
Example 8		*{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.41 $[MH]^+$436

Example 9		*{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.27 $[MH]^+$422
Example 10		*{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.52 $[MH]^+$450
Example 11		*{4-[4-(Ethyloxy)-9-methyl-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.11 $[MH]^+$ 390
Example 12		*[4-(1,3-Dioxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid*	Rt=3.69 $[MH]^+$ 416

Description 34

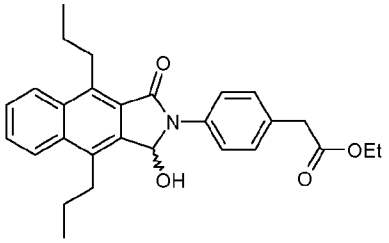
Ethyl {4-[4-(ethyloxy)-1-hydroxy-3-oxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate



Ethyl {4-[4-(ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D28) (350mg, 0.8mmol) was suspended in ethanol (10ml) and THF added in solution (20ml). Cooled to 0°C in an ice bath and treated with sodium borohydride (89mg, 2.4mmol) portionwise. Stirred at 0°C for 1 hour under argon. A further 3 equivalents of sodium borohydride were added portionwise and continued stirring for 1 hour. A further 9 equivalents were added over 6 hours until complete. Solvent evaporated and quenched with saturated ammonium chloride solution. Extracted with ethyl acetate (x3). Combined organics washed with water, brine, and dried over magnesium sulphate. Evaporated to give the title compound as a green oil, containing isomer shown in ~1:1 ratio (489mg, 1.1mmol).

LC/MS: Rt= 3.47, 3.54 $[MH]^+$ 448.

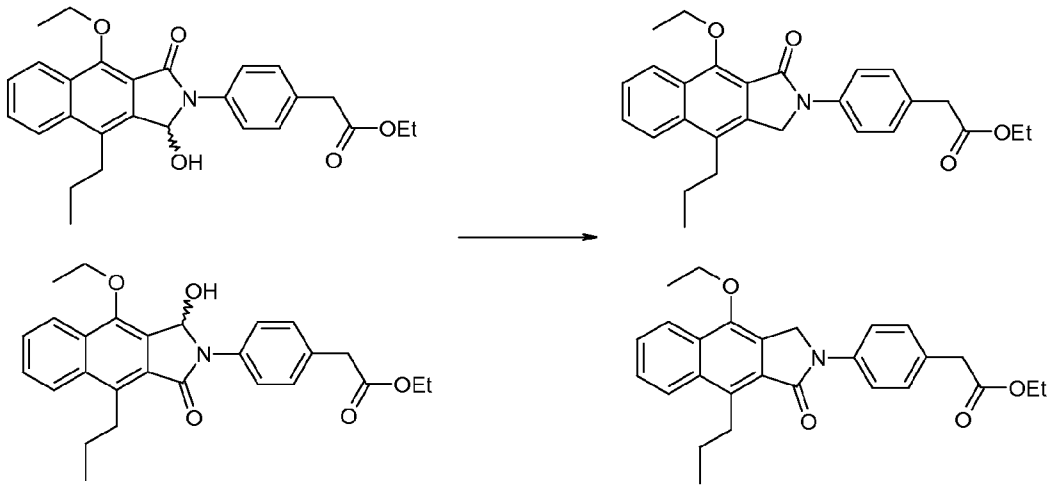
The following compound was prepared in a similar manner to Ethyl {4-[4-(ethyloxy)-1-hydroxy-3-oxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (D34) using the appropriate staring materials.

Description		Name	LC/MS
35		*Ethyl [4-(1-hydroxy-3-oxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-*	Rt=3.79 $[MH]^+$ 446

		2-yl)phenyl]acetate	

Description 36

Ethyl {4-[9-(ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate



Ethyl {4-[4-(ethyloxy)-1-hydroxy-3-oxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D34) and isomer mixture (489mg, 1.1mmol) was dissolved in TFA (10ml) and cooled in an ice bath to 0°C. Triethylsilane (0.26ml, 1.6mmol) was added dropwise and stirred for 10 minutes under argon at 0°C. Solvent evaporated and triturated in cold diethyl ether. Precipitate filtered to give a white solid. Isomers were separated using MDAP (shallow gradient 3.6-4.0).

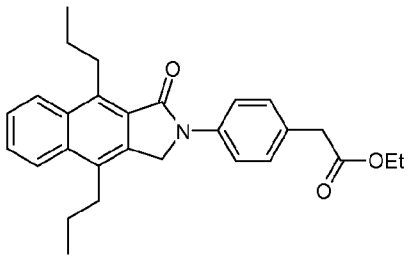
Fast eluting fractions were evaporated to give the title compound as a white solid (85mg, 0.20mmol).

LC/MS: Rt=4.03, $[MH]^+$ 432

Slow eluting fractions were evaporated to give ethyl {4-[4-(ethyloxy)-1-oxo-9-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate as a white solid (98mg, 0.22mmol).

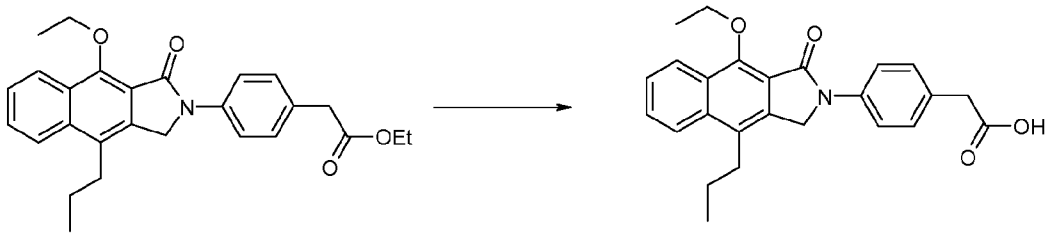
LC/MS: Rt=4.12, $[MH]^+$ 432

The following compound was prepared in a similar manner to Ethyl {4-[9-(ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (D36) using the appropriate staring materials.

Description		Name	LC/MS
37		*Ethyl [4-(1-oxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate*	Rt=4.21 $[MH]^+$ 430

Example 13

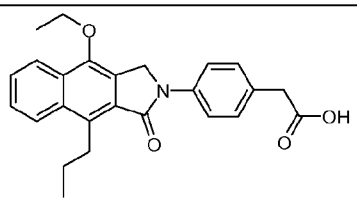
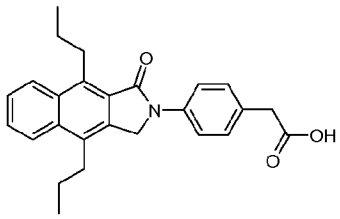
{4-[9-(Ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid



Ethyl {4-[9-(ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (D36) (85mg, 0.2mmol), was suspended in ethanol (20ml) and treated with 2N sodium hydroxide (5ml). Refluxed for 1 hour, then cooled to room temperature. Ethanol evaporated to dryness and water added. Acidified with 2N HCl. White precipitate was filtered, washed with water, collected and dried on vacuum oven to give the title compound as a white solid (65mg, 0.16mmol).

LC/MS: Rt=3.42, $[MH]^+$ 404

The following compounds were prepared in a similar manner to {4-[9-(ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetic acid (D15) using the appropriate staring materials.

		Name	LC/MS
Example 14		*{4-[4-(Ethyloxy)-1-oxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.47 $[MH]^+$404
Example 15		*[4-(1-Oxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid*	Rt= 3.75 $[MH]^+$ 402

Biological data

***In vitro* cAMP assay**

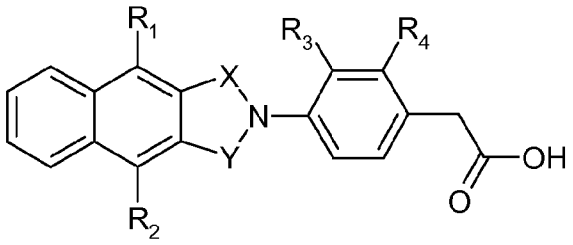
Studies were performed using HEK-293(T) cells expressing the recombinant human prostanoid EP_4 receptor (HEK-EP_4 cells). Cells were grown as a monolayer culture in DMEM-F12/F12 containing glutamax II (Gibco) and supplemented with 10% foetal bovine serum (Gibco) and 0.4mg.ml-1 G418. HEK-EP_4 cells were pre-treated 24hr and 30mins prior to the experiment with 10μM indomethacin and harvested using Versene containing 10μM indomethacin. The cells were resuspended in assay buffer (DMEM:F12, 10μM indomethacin and 200μM IBMX) at 1×10^6 cells per ml and incubated for 20min at 37°C. Thereafter, 50μl of cells were added to 50μl agonist (compound of Formula (I)) and incubated at 37°C for 4 minutes before stopping reactions with 100μl of 1% triton X-100. cAMP levels in the cell lysates were

determined using a competition binding assay. In this assay the ability of cell lysates to inhibit 3H-cAMP (Amersham) binding to the binding subunit of protein kinase A was measured and cAMP levels were calculated from a standard curve. The data for each compound were expressed as a % of the response to a 10nM maximal concentration of the standard agonist PGE2. For each compound the maximal response and concentration of compound causing 50% of its maximal response were calculated. Intrinsic activity is expressed relative to the maximal response to PGE2. Unless stated, reagents were purchased commercially from Sigma.

The Examples of the present invention were tested in the above-mentioned assay and exhibited average pEC_{50} values of 6.79 or higher, and average intrinsic activities of 24% or higher.

CLAIMS:

1. A compound of formula (I)



(I)

wherein,

R_1 represents C_{1-4} alkyl or C_{1-4} alkoxy;

R_2 represents C_{1-4} alkyl or C_{1-4} alkenyl;

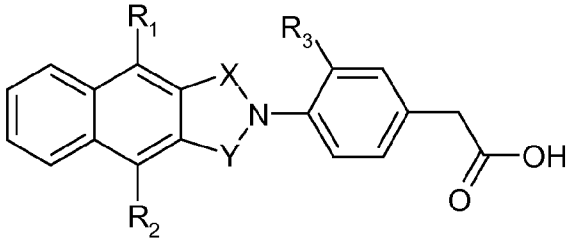
R_3 represents H, F, Cl, methyl, methoxy or CF_3;

R_4 represents H or F;

X represents CH_2 or C=O; and

Y represents CH_2 or C=O, provided that at least one of X and Y represents C=O and at least one of R_3 and R_4 is H, and pharmaceutically acceptable derivatives thereof.

2. A compound of formula (IA)



(IA)

wherein,

R_1 represents C_{1-4} alkyl or C_{1-4} alkoxy;

R_2 represents C_{1-4} alkyl or C_{1-4} alkenyl;

R_3 represents H or F;

X represents CH_2 or C=O; and

Y represents CH_2 or C=O, provided that at least one of X and Y represents C=O, and pharmaceutically acceptable derivatives thereof.

3. A compound of formula (I) which is selected from:

{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-Ethenyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methyl-1-propen-1-yl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-1,3-dioxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-Ethyl-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-(Ethyloxy)-9-(2-methylpropyl)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid,

{4-[4-(Ethyloxy)-9-methyl-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

[4-(1,3-Dioxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid,

{4-[9-(Ethyloxy)-1-oxo-4-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid,

{4-[4-(Ethyloxy)-1-oxo-9-propyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid, and

[4-(1-Oxo-4,9-dipropyl-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetic acid,

and pharmaceutically acceptable derivatives thereof.

4. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 for use in human or veterinary medicine.

5. A compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 for use in the treatment of a condition which is mediated by the action, or loss of action, of PGE_2 at EP_4 receptors.

6. A method of treating a human or animal subject suffering from a condition which is mediated by the action, or by loss of action, of PGE_2 at EP_4 receptors which comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3.

7. A method of treating a human or animal subject suffering from a pain, or an inflammatory, immunological or bone disease, a neurodegenerative disease or a kidney dysfunction, which method comprises administering to said subject an effective amount of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3.

8. Use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment of a condition which is mediated by the action of PGE_2 at EP_4 receptors.

9. Use of a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 for the manufacture of a medicament for the treatment or prevention of a condition such as a pain, or an inflammatory, immunological, bone, neurodegenerative or kidney disorder.

10. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 adapted for use in human or veterinary medicine.

11. A combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof as claimed in any one of claims 1 to 3 together with a further therapeutic agent or agents.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/060313

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/64 C07D209/66 A61K31/4035 A61P25/00 A61P35/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/064564 A (GLAXO GROUP LTD [GB]; CONGREVE MILES STUART [GB]; GIBLIN GERARD MARTIN) 22 August 2002 (2002-08-22) cited in the application page 1, line 1 - line 25 claim 1	1-11
Y	EP 1 442 744 A (GLAXO GROUP LTD [GB]) 4 August 2004 (2004-08-04) page 6, paragraph 21; compound IF	1-11

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 November 2008	09/12/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bissmire, Stewart

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/060313

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	RUFER C ET AL: "NEUE ACYLIERTE 2-(4-AMINOPHENYL)-PROPIONSAEUREN ALS POTENTIELE ANTIPHLOGISTICA" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 13, no. 2, 1 March 1978 (1978-03-01), pages 193-198, XP001068547 ISSN: 0223-5234 page 195; table II; compound 6B abstract ----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/060313

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02064564 A	22-08-2002	AT 365715 T	15-07-2007
		DE 60220890 T2	28-02-2008
		EP 1368312 A1	10-12-2003
		ES 2288547 T3	16-01-2008
		JP 2004520400 T	08-07-2004
		US 2008234358 A1	25-09-2008
		US 2005080257 A1	14-04-2005
		US 2007088068 A1	19-04-2007
EP 1442744 A	04-08-2004	NONE	