BENZOISOINDOLE DERIVATIVES 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 in *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*

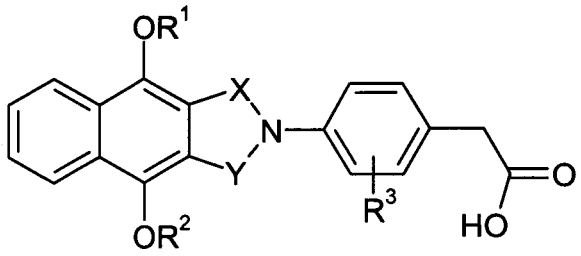
Research 2005, 1066(1-2), 71-77 that an EP_4 receptor agonist (ONO-AE1-329) protects against neurotoxicity in an acute model of excitotoxicity in the brain.

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



(I)

wherein,

R^1 and R^2 independently represent C_{1-4} alkyl or difluoromethyl provided that at least one of R^1 and R^2 represents difluoromethyl;

R^3 represents H, F, Cl or Br; and

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

In one embodiment of the invention one of R^1 and R^2 represents C_{1-4} alkyl and the other represents difluoromethyl. In one embodiment of the invention one of R^1 and R^2 represents methyl and the other represents difluoromethyl. In one embodiment of the invention one of R^1 and R^2 represents ethyl and the other represents difluoromethyl. In one embodiment of the invention one of R^1 and R^2 represents n-propyl and the other represents difluoromethyl. In one embodiment of the invention one of R^1 and R^2 represents *iso*-propyl and the other represents difluoromethyl. In another embodiment of the invention both R^1 and R^2 represent difluoromethyl.

In one embodiment of the invention R^3 represents F. In another embodiment of the invention R^3 represents Cl. In another embodiment of the invention R^3 represents H. In another embodiment of the invention R^3 represents H, F or Cl. In another embodiment of the invention R^3 represents F or Cl.

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

In another embodiment of the invention there is provided a compound of formula (I) selected from the group consisting of:

(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

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

{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;

(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;

4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetic acid;
{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;
(3-Chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetic acid;
(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetic acid;
(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-2-fluorophenyl)acetic acid; or a pharmaceutically acceptable derivative thereof.

The present invention covers all combinations of particular and preferred embodiments as described herein.

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, butyl and *iso*-butyl. The term 'C_{1-6} alkyl' may be interpreted accordingly.

As used herein the term difluoromethyl means -CHF_2.

As used herein F means fluoro, Cl means chloro and Br means bromo.

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. In one embodiment of the invention pharmaceutically acceptable derivative means salt, solvate or ester, or salt or solvate of such ester. In another embodiment of the invention pharmaceutically acceptable derivative means salt or ester, or salt of such ester.

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 compound 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 the general formula (I). These may be formed by esterification of the carboxylic acid group in the parent compound of general 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 the present invention, in particular 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, more suitably at least 75% pure and preferably 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). Preferably, 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. 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. 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 in formula (I) 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, fluorine and chlorine, such as 2H, 3H, 11C, 13C, 14C, 15N, 17O, 18O, 18F and 36Cl.

Isotopically-labelled compounds of the present invention, 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 the invention 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 reference to treatment includes both treatment of established symptoms and prophylactic treatment.

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

According to another 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.

According to a 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.

According to a further 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.

According to another 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.

According to another 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.

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 the invention 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 the invention 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 EP_4 receptor compounds for use in the present invention 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; EP1 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.

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. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

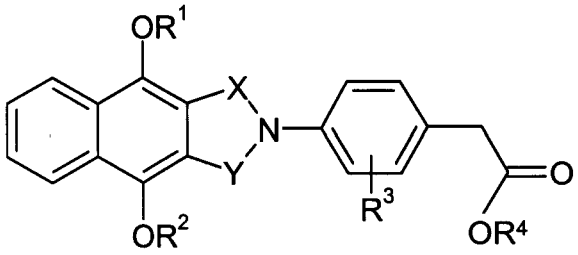
When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those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

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.

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 compounds of formula (I) and pharmaceutically acceptable derivatives thereof.

Thus, in one embodiment of the invention there is provided a process for preparing a compound of formula (I) wherein one of X and Y represents C=O and the other represents CH_2, and R^1, R^2 and R^3 are as hereinbefore defined in relation to formula (I), which process comprises reacting a compound of formula (II),

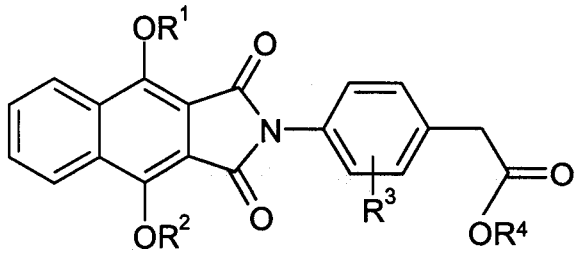


(II)

wherein, one of X and Y represents C=O and the other represents CH_2; R^1, R^2 and R^3 are as hereinbefore defined in relation to formula (I); and R^4 represents C_{1-6} alkyl; with a suitable base, such as sodium hydroxide, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

In one embodiment the above-mentioned reaction comprising a compound of formula (II) is performed in a suitable solvent, such as ethanol, under reflux.

In another embodiment of the present invention there is provided a process for preparing a compound of formula (I), wherein X and Y represent C=O and R^1, R^2 and R^3 are as hereinbefore defined in relation to formula (I), which process comprises adding a compound of formula (III),



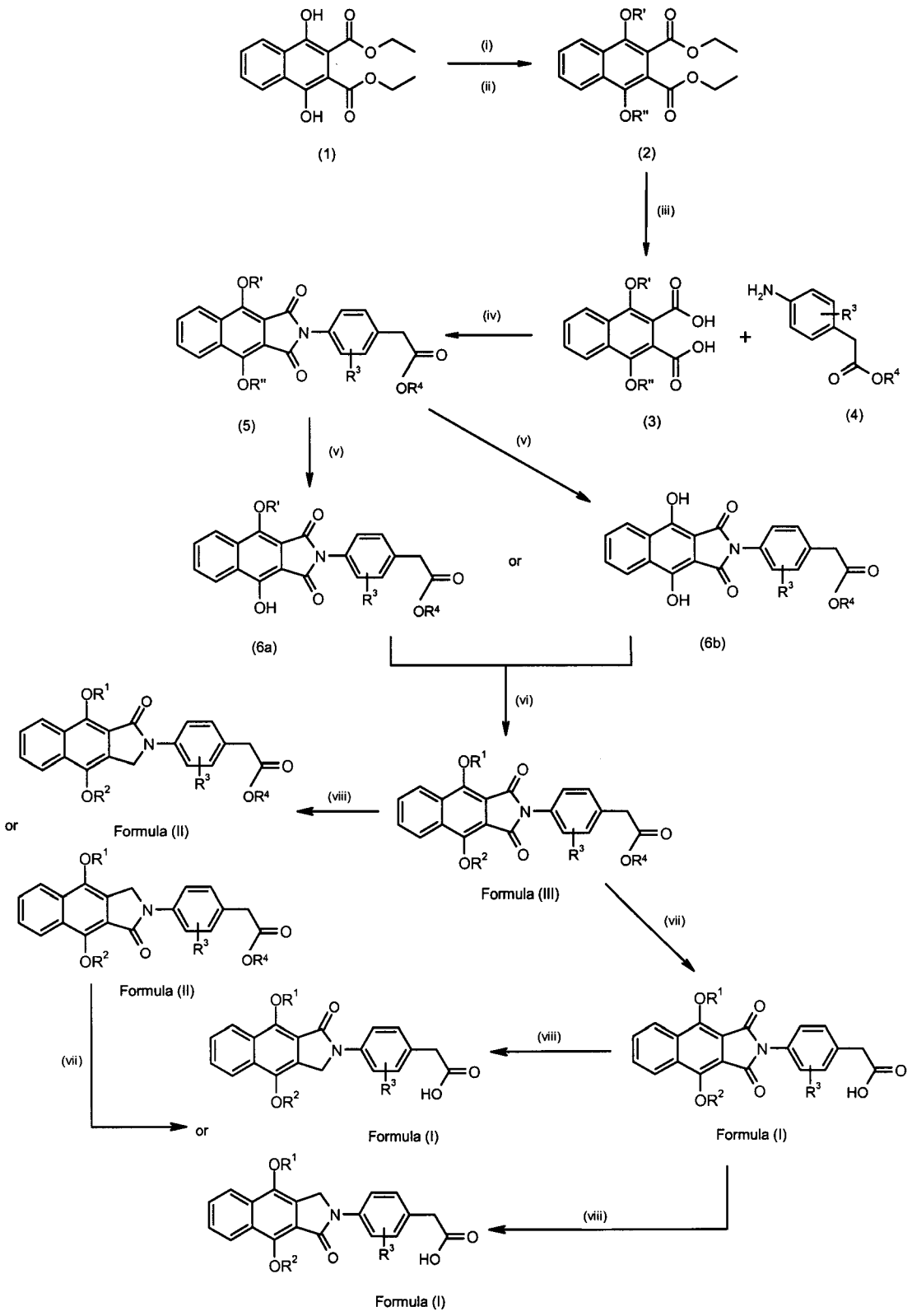
(III)

wherein, R^1, R^2 and R^3 are as hereinbefore defined in relation to formula (I); and R^4 represents C_{1-6} alkyl; to a suitable acid or mixture of acids, such as glacial acetic acid in the presence of hydrochloric acid, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

In one embodiment the above-mentioned reaction comprising a compound of formula (III) is performed at a temperature in the range from about 50 to 110 °C, for a time period in the range from about 2 to 70 hours. In one embodiment, the molar ratio of glacial acetic acid to acid, such as hydrochloric acid, present in the reaction mixture is 1:1.

Compounds of formula (II) and (III) may be prepared according to Scheme 1 below:

Scheme 1

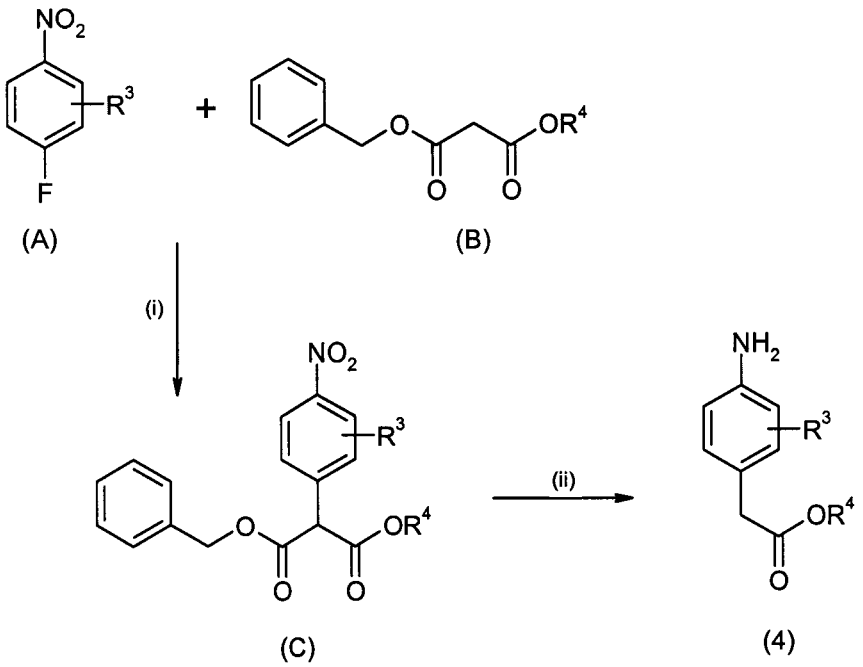

(1)
(2)
(3)
(4)
(5)
(6a)
(6b)
Formula (II)
Formula (III)
Formula (I)
Formula (I)
Formula (II)
Formula (I)
Formula (I)
(i)
(ii)
(iii)
(iv)
(v)
(v)
or
(vi)
(vii)
(viii)
or
(vii)
(viii)
(viii)

(i) R'-Br, K_2CO_3, $(CH_3)_2CO$; (ii) R''-Br, K_2CO_3, $(CH_3)_2CO$; (iii) NaOH, $EtOH/H_2O$; (iv) CH_3CO_2H; (v) Pd/C, H_2, EtOH or BBr_3, CH_2Cl_2; (vi) $CClF_2CO_2Na$, Na_2CO_3, DMF; or $CHClF_2$, K_2CO_3, KI, DMF; (vii) NaOH, EtOH or HCl, CH_3CO_2H ; (viii) $NaBH_4$, MeOH or EtOH then TFA, Et_3SiH; (wherein R' and R'' may be the same or different and represent suitable protecting groups such as $-CH_2Ph$, or one of R' and R'' represents a suitable protecting group and the other represents R^1 or R^2).

Compound (1) may be prepared in accordance with the method disclosed in International Patent Application, Publication Number WO 02/064564.

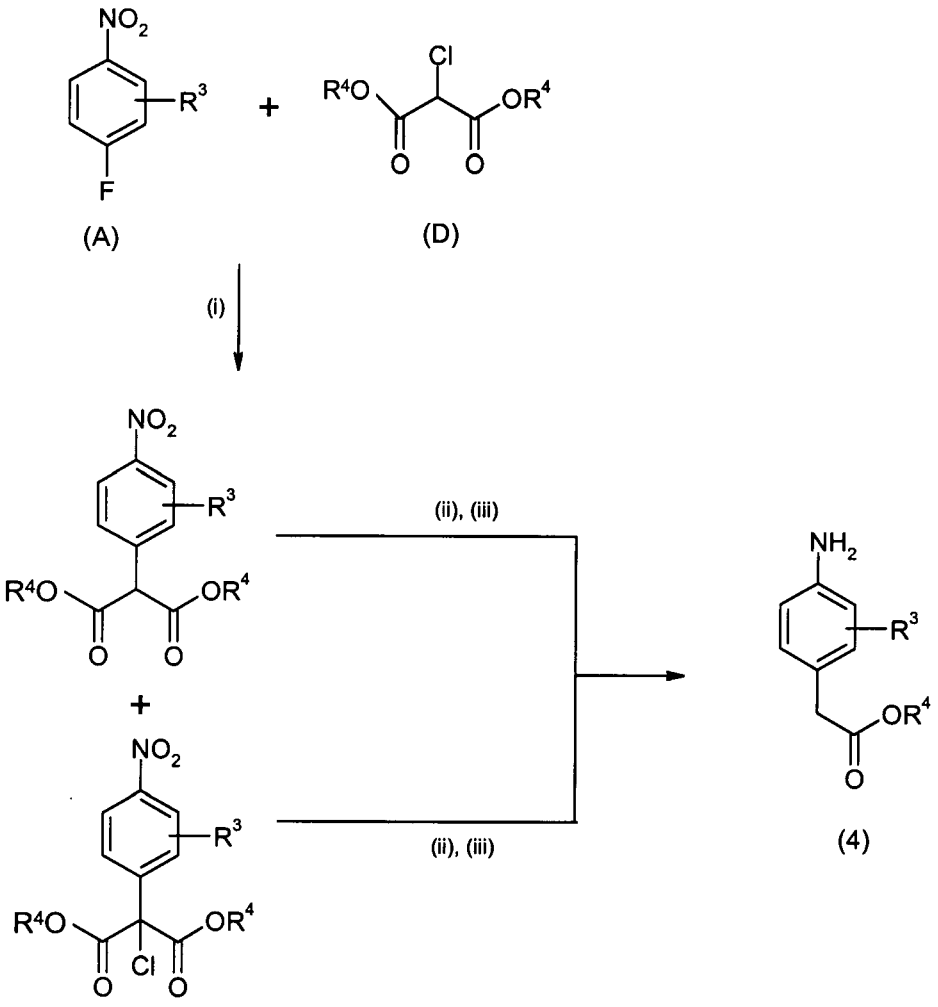
Compounds of formula (4) where R^3 is F and R^4 is as hereinbefore defined in relation to formulae (II) and (III) may be prepared according to Schemes 2 and 3 below:

Scheme 2



(i) NaH, dry DMF; (ii) NH_4CO_2H, EtOH, Pd/C.

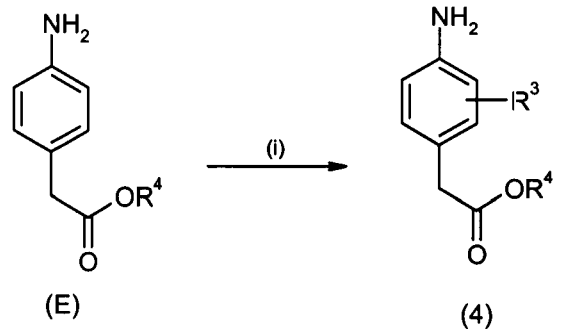
Scheme 3



(i) NaOH, dry DMF; (ii) NH_4CO_2H, EtOH, Pd/C; (iii) NaOH, H_2O, EtOH.

Compounds of formula (4) where R^3 is Br or Cl and R^4 is as hereinbefore defined in relation to formulae (II) and (III) may be prepared according to Scheme 4 below:

Scheme 4



(E) (4)

(i) N-Chlorosuccinamide or N-Bromosuccinamide.

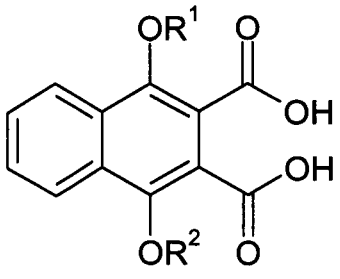
Compounds of formula (A) are commercially available or may be prepared in accordance with methods known in the art (for example, 3,4-difluoronitrobenzene may be purchased from Sigma-Aldrich Co. Ltd.).

Compounds of formula (B) are commercially available or may be prepared in accordance with methods known in the art (for example, benzyl ethyl malonate may be purchased from Sigma-Aldrich Co. Ltd.).

Compounds of formula (D) are commercially available or may be prepared in accordance with methods known in the art (for example, diethylchloromalonate may be purchased from Sigma-Aldrich Co. Ltd).

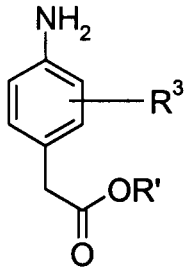
Compounds of formula (E) are commercially available or may be prepared in accordance with methods known in the art (for example, ethyl 4-aminophenyl acetate may be purchased from Avocado Research).

In another embodiment of the invention there is provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (IV),



(IV)

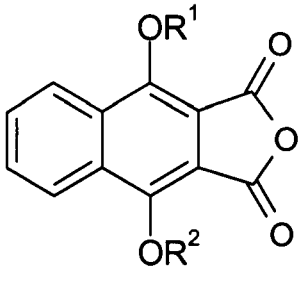
wherein R^1 and R^2 are as hereinbefore defined in relation to formula (I), with a compound of formula (V),



(V)

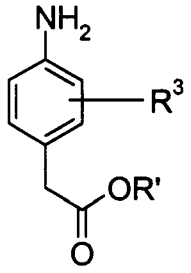
wherein R^3 is as hereinbefore defined in relation to formula (I) and R' represents H or C_{1-6} alkyl, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

In another embodiment of the invention there is provided a process for preparing a compound of formula (I) or a pharmaceutically acceptable derivative thereof, which process comprises reacting a compound of formula (VI),



(VI)

wherein R^1 and R^2 are as hereinbefore defined in relation to formula (I), with a compound of formula (V),



(V)

wherein R^3 is as hereinbefore defined in relation to formula (I) and R' represents H or C_{1-6} alkyl, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

Compounds of formula (IV), (V) and (VI) are commercially available or may be prepared in accordance with methods known in the art

The following Descriptions and Examples illustrate the preparation of the compounds of the invention. Descriptions refer to intermediate compounds.

Abbreviations

DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EtOH	Ethanol
LC/MS	Liquid chromatography/Mass spectroscopy
MDAP	Mass Directed Auto Preparation
MeOH	Methanol
TFA	Trifluoroacetic acid

Analytical procedures

LC/MS

Column

Waters Atlantis (4.6mm x 50mm). Stationary phase particle size, 3μm.

Solvents

A: Aqueous solvent = Water + 0.05% Formic Acid

B: Organic solvent = Acetonitrile + 0.05% Formic Acid

Method

.

Time / min	%B
0	3
0.1	3
4	97
4.8	97
4.9	3
5.0	3

- Flow rate, 3ml/mins.
- Injection volume, 5μl.
- Column temperature, 30°C.
- UV detection range, 220 to 330nm.

All retention times are measured in minutes.

NMR

^{1}H NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer or a Bruker DPX250 NMR spectrometer. Chemical shifts are expressed in parts per million (ppm, δ units). Coupling constants (*J*) are in units of hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d

(doublet), t (triplet), q (quartet), dd (double doublet), ddd (double, double doublet), dt (double triplet), m (multiplet), br (broad).

Purification Techniques

Purification of the Examples may be carried out by conventional methods such as chromatography and/or recrystallisation using suitable solvents. Chromatographic methods include column chromatography, flash chromatography, HPLC (high performance liquid chromatography), SFC (supercritical fluid chromatography), and MDAP (mass directed autopreparation).

The term "Biotage" when used herein refers to commercially available pre-packed silica gel cartridges.

Mass Directed Auto Preparation (MDAP)

Column

Waters Atlantis: 19mm x 100mm (small scale); and 30mm x 100mm (large scale).

Stationary phase particle size, 5μm.

Solvents

A: Aqueous solvent = Water + 0.1% Formic Acid

B: Organic solvent = Acetonitrile + 0.1% Formic Acid

Make up solvent = Methanol : Water 80:20

Needle rinse solvent = Methanol

Methods

Five methods were used depending on the analytical retention time of the compound of interest:

(1) Large/Small Scale 1.0-1.5 = 5-30% B

(2) Large/Small Scale 1.5-2.2 = 15-55% B

(3) Large/Small Scale 2.2-2.9 = 30-85% B

(4) Large/Small Scale 2.9-3.6 = 50-99% B

Runtime, 13.5 minutes, comprising 10-minute gradient followed by a 3.5 minute column flush and re-equilibration step.

(5) Large/Small Scale 3.6-5.0 = 80-99% B

Runtime, 13.5 minutes, comprising 6-minute gradient followed by a 7.5 minute column flush and re-equilibration step.

Flow rate

20mls/min (Small Scale) or 40mls/min (Large Scale).

Specification of HPLC purification system:

- Column: Supelco LCABZ++, 100mm x 20mm ID, particle size 5µm
- Flow rate: 20ml/min
- Injection volume: 0.5ml
- Temp: RT
- Solvents: A - Aqueous solvent = Water + 0.1% Formic Acid; B - Organic solvent = MeCN/Water 95:5 +0.05% Formic Acid
- Run time: 9 min gradient followed by 5 min column flush and re-equilibration
- Gradient: 30-80% B

SFC (Super Critical Fluid Chromatography)

Column:	Chiralcel OD-H S.F.C. (250 mm x 21.2mm ID; 5 micron particle size) or Ethyl-pyridine column (150 mm length x 21.2 mm ID; 6 micron particle size) or Chiralpak AD (355 and 438) (250 mm length x 21.2 mm ID; 10 micron particle size)
Mobile phase:	A = Carbon dioxide (supercritical) B = Methanol A:B (70:30 - 85:15 w/w isocratic)
Flow-rate:	39.4 gmin-1 (= 50 mLmin-1 approx.)
Temperature:	40 'C

Back pressure:	100 bar
Detection:	U.V. absorbance at 215 nm
Run-time:	25 minutes or 20 minutes
Sample concentration:	100 mgmL-1 in dimethylformamide
Injection volume:	VARIABLE

HPLC purification 1

Stationary phase:	Chiralcel OD
	(250 mm length x 21.2 mm ID; 10 micron particle size)
Mobile phase:	Heptane : Ethanol
	(ranging from 50:50 v/v isocratic to 90:10 v/v isocratic)
	320 = 50:50 v/v
	353 = 70:30 v/v
	354 = 90:10 v/v
	356 = 70:30 v/v
Flow-rate:	17 mLmin-1
Temperature:	Ambient
Detection:	U.V. absorbance at 215 nm
Injection volume:	0.9 mL

HPLC purification 2

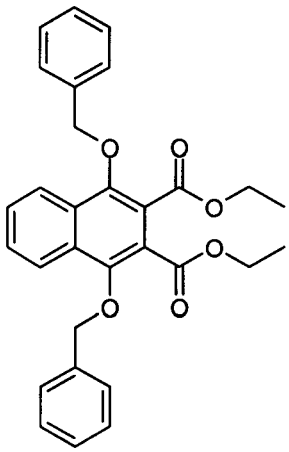
Column:	Phenomenex Luna C18 (2) (50 mm x 21.2mm ID;
	10 micron particle size)
Mobile phase:	A = Acetonitrile + 0.1% v/v trifluoroacetic acid
	B = Water + 0.1% v/v trifluoroacetic acid
	(Gradient and isocratic methodologies)
Flow-rate:	20 mLmin-1 approx.
Temperature:	Ambient
Detection:	U.V. absorbance at 215 nm (0 nm band-width)

Sample concentration: 100 mgmL-1 in dimethylformamide
Injection volume: VARIABLE

ID = internal diameter

Description 1

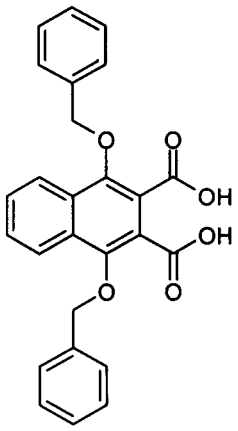
Diethyl 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate



Benzylbromide (2.95ml, 24.7mmol) was added to a stirred solution of diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (3g, 9.87mmol) and potassium carbonate (3.40g, 24.7mmol) in acetone (100ml). The reaction mixture was refluxed for 18 hours under an atmosphere of argon. The resulting mixture was evaporated and the reaction mixture triturated with water. The resulting tan coloured solid was collected by filtration and washed with water then dried under vacuum to give the title compound (5.23g, 10.8mmol). LC/MS: Rt=4.13, $[MH]^+$ 485.

Description 2

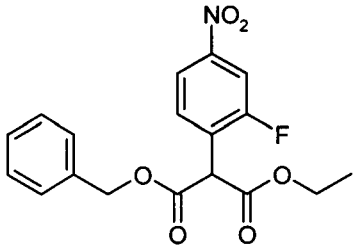
1,4-Bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid



A mixture of diethyl 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate (4.78g, 9.88mmol), ethanol (75ml), and 2N aqueous sodium hydroxide solution (75ml) was refluxed for 2 hours. The reaction mixture was cooled and evaporated. This was acidified with HCl (2N) and the resulting cream solid was collected by filtration and washed with water. This was dried under vacuum to give the title compound (3.79g, 8.86mmol). LC/MS: Rt=3.15, $[MH]^-$ 427.

Description 3

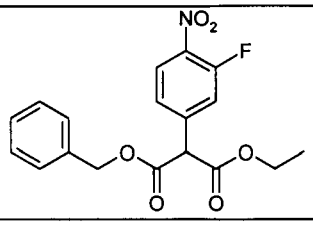
Ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate



Sodium hydride (504mg, 12.6mmol) was added portionwise to an ice bath chilled solution of benzyl ethyl malonate (2.9g, 12.6mmol) in dry DMF (20ml) and stirred for 10 minutes. At room temperature 3,4-difluoronitrobenzene (2g, 12.6mmol) was added and stirred under argon. Heated at 100°C for 20 hours. The reaction mixture was cooled and partitioned between 2N Hydrochloric acid (75ml) and ethyl acetate (75ml). The aqueous layer was extracted with ethyl acetate (2x 75ml) and the combined organics were evaporated to a yellow oil. Purified by

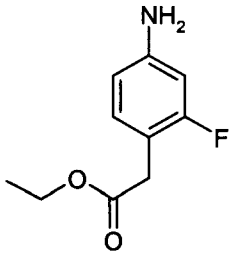
chromatography on silica gel eluting with ethyl acetate/hexane (1:4) to give the title compound as a yellow oil (3.86g, 10.6mmol). LC/MS: Rt=3.40, $[MH]^+$ 362.

The following compound was prepared in a similar manner to ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate using the appropriate starting materials.

	Name	LC/MS
	*Ethyl phenylmethyl (3-fluoro-4-nitrophenyl)propanedioate*	Rt=3.30 $[MH]^+$ 362

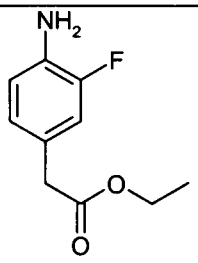
Description 4

Ethyl (4-amino-2-fluorophenyl)acetate



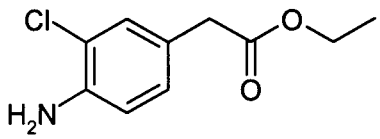
Ethyl phenylmethyl (2-fluoro-4-nitrophenyl)propanedioate (3.86g, 10.6mmol) dissolved in ethanol, was treated with ammonium formate (6.7g, 10.6mmol) and palladium on carbon 10% paste (380mg) was added under argon. The reaction mixture was refluxed for 3 hours, cooled and filtered. Evaporated and purified by chromatography on silica gel eluting with ethyl acetate/hexane (1:1) to give the title compound as a yellow oil (1.26g). LC/MS: Rt=2.10, $[MH]^+$ 198.

The following compound was prepared in a similar manner to ethyl (4-amino-2-fluorophenyl)acetate, using the appropriate starting materials.

	Name	LC/MS
	*Ethyl (4-amino-3-fluorophenyl)acetate*	Rt=2.20 $[MH]^+$ 198

Description 5

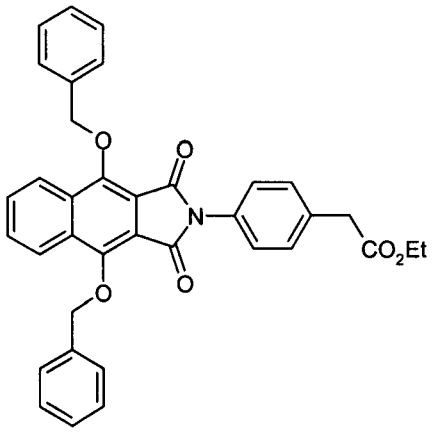
Ethyl (4-amino-3-chlorophenyl)acetate



Ethyl-4-aminophenylacetate (20g, 112mmol) was dissolved in chloroform (300ml) and treated with N-chlorosuccinimde (14.92g, 112mmol) and stirred for 15 minutes at room temperature under argon. Reaction mixture was washed with water, brine and dried over magnesium sulphate. Evaporated to a brown oil which was purified by chromatography on silica gel eluting with ethyl acetate (0-45%) in hexane to give the title compound as a orange oil (10.12g, 47.4mmol). LC/MS: Rt=2.59, $[MH]^+$ 214.

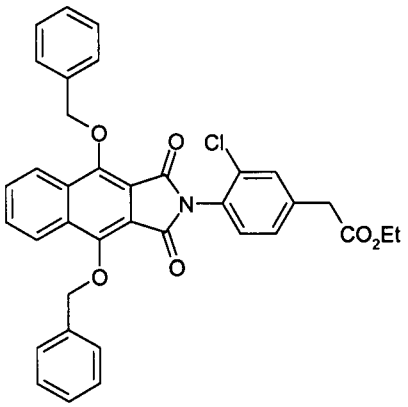
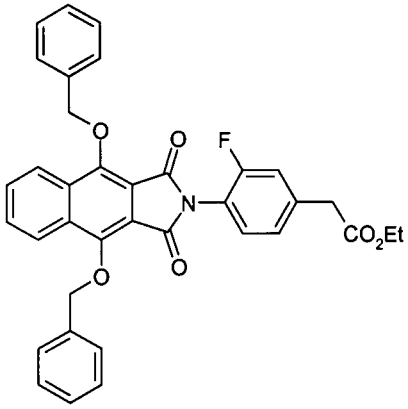
Description 6

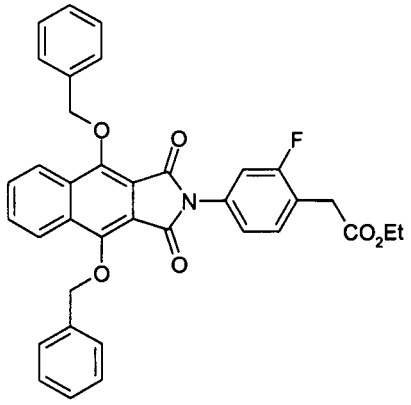
Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



A mixture of 1,4-bis[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (2.0g, 4.67mmol) and ethyl (4-aminophenyl)acetate (1.67g, 9.35mmol) were heated to 120°C in acetic acid (30ml) for 2 hours. The mixture solidified on standing at room temperature overnight. Water was added and the solid collected by filtration and washed with water. This was dried under vacuum to give the title compound (2.65g, 4.64mmol). LC/MS: Rt=4.24, $[MH]^+$ 572.

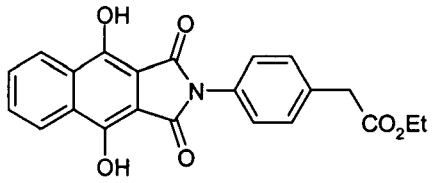
The following compounds were prepared in a similar manner to ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

	Name	LC/MS
	*Ethyl (3-chloro-4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=4.15 $[MH]^+$606
	*Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=4.08 $[MH]^+$ 590

	*Ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy] -1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*	Rt=4.10 $[MH]^+$590

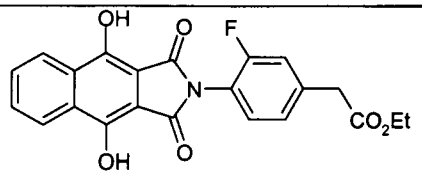
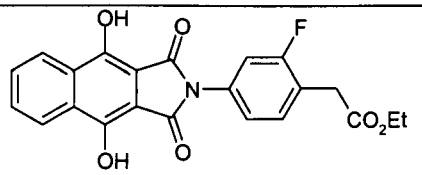
Description 7

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



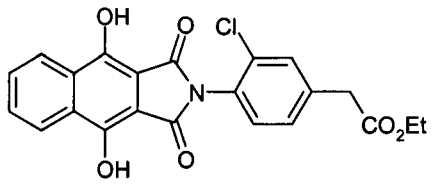
10% Palladium on carbon (0.265g) was suspended in ethanol (250ml), to this was added ethyl (4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (2.65g, 4.64mmol). The reaction was stirred at room temperature under an atmosphere of hydrogen for 3 hours. This was filtered through a bed of celite under a blanket of argon, and washed with dichloromethane. The filtrate was evaporated to give a tan solid (1.52g, 3.89mmol). LC/MS: Rt=3.25, $[MH]^+$ 392.

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

	Name	LC/MS
	*Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-fluorophenyl]acetate*	Rt=3.16 $[MH]^+$ 410
	*Ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-2-fluorophenyl]acetate*	Rt=3.24 $[MH]^+$ 410

Description 8

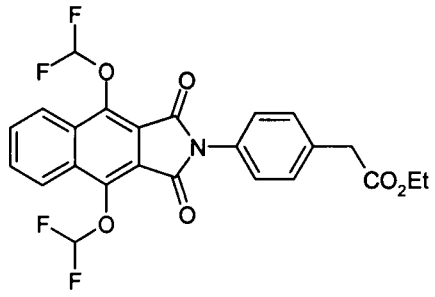
Ethyl [3-chloro-4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)phenyl]acetate



To a solution of ethyl (3-chloro-4-{1,3-dioxo-4,9-bis[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (0.505g, 0.84mmol) in DCM (30ml), cooled to -78°C under an atmosphere of argon, was added boron tribromide (0.24ml, 2.50mmol) drop wise. Stirred at -78°C for 25 minutes. The reaction mixture was quenched with water and warmed to room temperature. This was extracted twice with DCM using a hydrophobic frit. The organic phase was evaporated to an orange solid. Hot trituration in DCM resulted in a yellow solid which was collected by filtration (0.189g, 0.44mmol). The filtrate was purified by chromatography on silica gel, eluting with ethyl acetate (0-70%) in hexane to give the title compound as a yellow solid (0.035g, 0.082mmol). LC/MS: Rt=3.22, $[MH]^+$ 426.

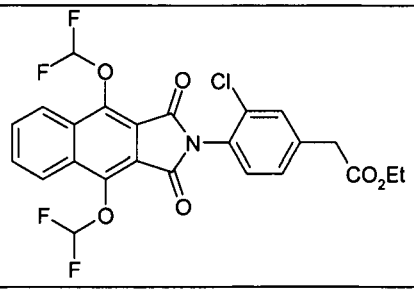
Description 9

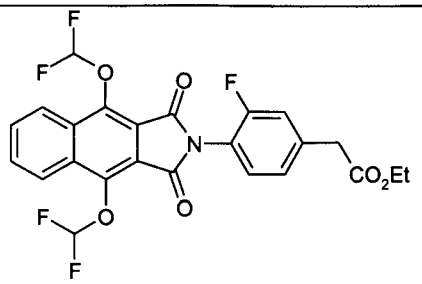
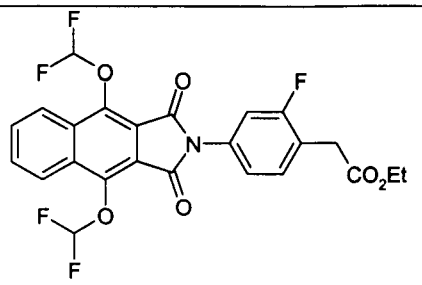
Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



To a solution of ethyl [4-(4,9-dihydroxy-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)phenyl]acetate (0.200g, 0.51mmol) in dimethylformamide (7ml) was added sodium carbonate (0.163g, 1.53mmol) followed by sodium chlorodifluoroacetate (0.233g, 1.53mmol). The mixture was heated to 100°C for 2.5 hours. Further sodium carbonate (0.054g, 0.51mmol) and sodium chlorodifluoroacetate (0.078g, 0.51mmol) was added, heating continued for 1 hour, and the same amounts added again and heating continued for 30 minutes. The mixture was cooled to room temperature and water added. The resulting brown solid was collected by filtration and washed with water. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as white solid (0.032g, 0.065mmol). LC/MS: Rt=3.61, $[MH]^+$ 492.

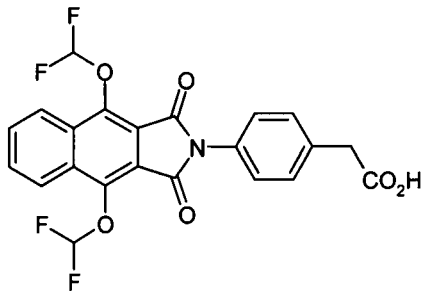
The following compounds were prepared in a similar manner to ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

	Name	LC/MS
	*Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetate*	Rt=3.64 $[MH]^+$526

	*Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.61 $[MH]^+$ 510
	*Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*	Rt=3.63 $[MH]^+$ 510

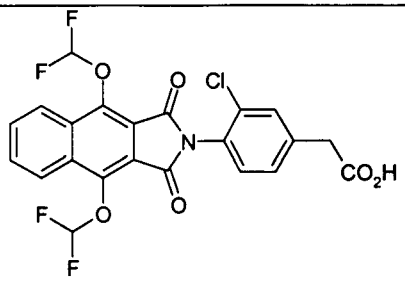
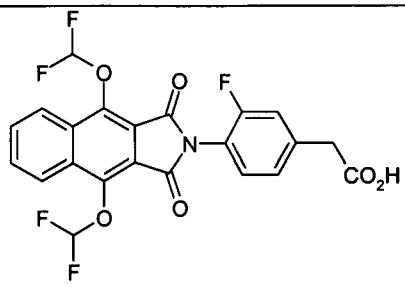
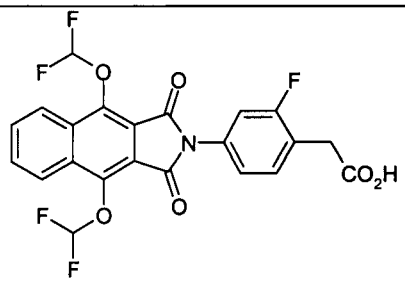
Example 1

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



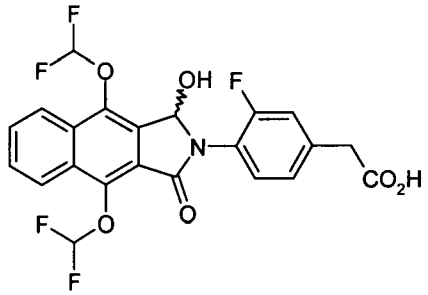
Ethyl (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (0.03g, 0.061mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (4ml) for 2 hours. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration and washed with water. This was purified by MDAP to give the desired product (0.017g, 0.037mmol). LC/MS: Rt=3.28, $[MH]^+$ 464.

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

		Name	LC/MS
Example 2		*(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid*	Rt=3.23 $[MH]^+$498
Example 3		*(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid*	Rt=3.15 $[MH]^+$ 482
Example 4		*(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.18 $[MH]^+$482

Description 10

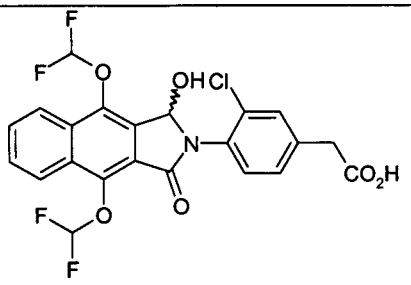
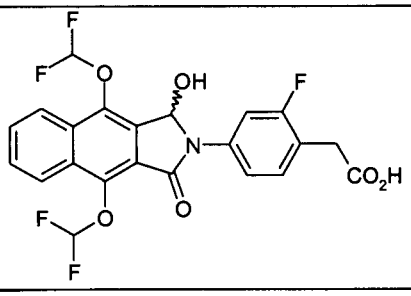
(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid



To a solution of (4-{4,9-bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid (0.041g, 0.085mmol) in ethanol (2ml) and tetrahydrofuran (4ml), was added sodium borohydride (0.019g,

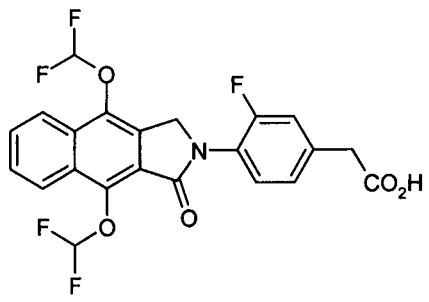
0.51mmol). This was stirred at 0°C for 5 minutes. The mixture was evaporated and then quenched with aqueous saturated ammonium chloride solution until the mixture was pH7. This was extracted x 2 with ethyl acetate, washed with brine, dried over magnesium sulphate and evaporated to give the crude product (0.035g, 0.072mmol). LC/MS: Rt=2.88, $[MH]^+$484.

The following compounds were prepared in a similar manner to (4-{4,9-bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid using the appropriate starting materials.

	Name	LC/MS
	*(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid*	Rt=2.95 $[MH]^+$500
	*(4-{4,9-Bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.03 $[MH]^+$ 484

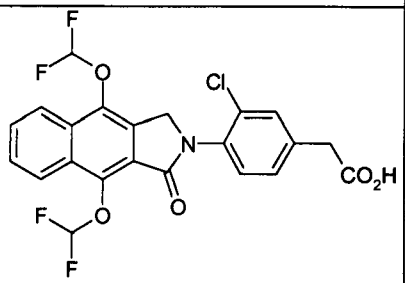
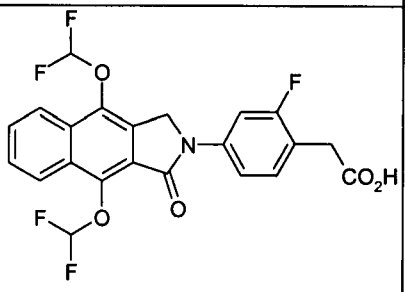
Example 5

(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid



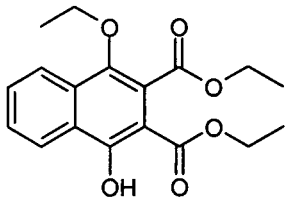
To a solution of (4-{4,9-bis[(difluoromethyl)oxy]-1-hydroxy-3-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid (0.035g, 0.072mmol) in trifluoroacetic acid (2ml) cooled to 0°C, was added triethylsilane (0.019ml, 0.110mmol). Stirring continued at 0°C for 5 minutes and then the mixture was evaporated. The crude mixture was purified using MDAP. The clean fractions were evaporated to give the title compound (0.015g, 0.033mmol). LC/MS: Rt=3.15, $[MH]^+$468.

The following compounds were prepared in a similar manner to (4-{4,9-bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid using the appropriate starting materials.

		Name	LC/MS
Example 6		*(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid*	Rt=3.21 $[MH]^+$484
Example 7		*(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.27 $[MH]^+$ 468

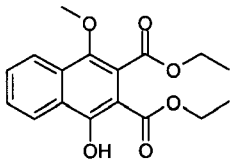
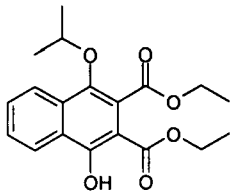
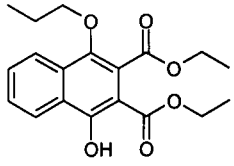
Description 11

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



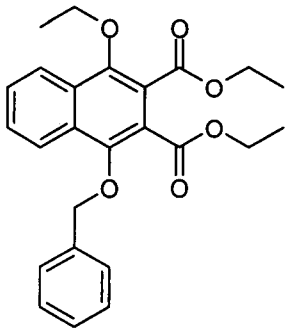
Bromoethane (0.359g, 3.29mmol) was added to a stirred solution of diethyl 1,4-dihydroxy-2,3-naphthalenedicarboxylate (1g, 3.29mmol) and potassium carbonate (0.454g, 3.29mmol) in acetone (25ml). The reaction mixture was refluxed for 24 hours under an atmosphere of argon. The resulting mixture was evaporated and the residue was partitioned between 2 x ethylacetate and water. The combined organics were washed with water and dried over magnesium sulphate. The orange oil was purified by chromatography on silica gel, eluting with ethyl acetate (0-10%) in hexane to give the title compound as a clear oil (0.661g, 1.99mmol). LC/MS: Rt=3.63, $[MH]^-$ 331.

The following compounds were prepared in a similar manner to diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate using the appropriate starting materials.

	Name	LC/MS
	*Diethyl 1-hydroxy-4-(methyloxy)-2,3-naphthalenedicarboxylate*	Rt=3.50 $[MH]^-$317
	*Diethyl 1-hydroxy-4-[(methylethoxy]-2,3-naphthalenedicarboxylate*	Rt=3.69 $[MH]^-$ 345
	*Diethyl 1-hydroxy-4-(propyloxy)-2,3-naphthalenedicarboxylate*	Rt=3.80 $[MH]^-$ 345

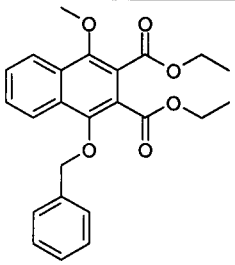
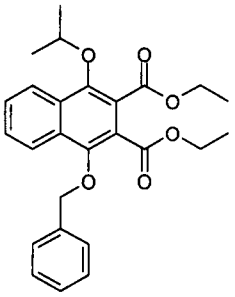
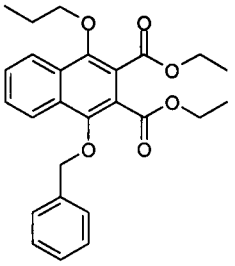
Description 12

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



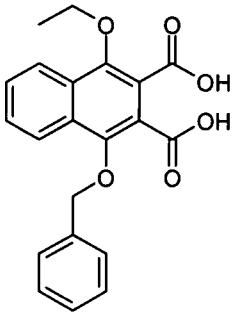
Benzyl bromide (1.32ml, 11.1mmol) was added to a stirred solution of diethyl 1-(ethyloxy)-4-hydroxy-2,3-naphthalenedicarboxylate (2.45g, 7.38mmol) and potassium carbonate (1.53g, 11.1mmol) in acetone (50ml). The reaction mixture was refluxed for 1 hour under an atmosphere of argon. The resulting mixture was evaporated and the residue was partitioned between 2 x ethylacetate and brine. The combined organics were washed with water and dried over magnesium sulphate. The clear oil was purified by chromatography on silica gel, eluting with ethyl acetate (0-40%) in hexane to give the title compound as clear oil (3.05g, 7.23mmol). LC/MS: Rt=3.77, $[MH]^+$ 423.

The following compounds were prepared in a similar manner to diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate using the appropriate starting materials.

	Name	LC/MS
	*Diethyl 1-(methyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate*	Rt=3.80 $[MH]^+$409
	*Diethyl 1-[methylethoxy]-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate*	Rt=3.83 $[MNH_4]^+$ 454
	*Diethyl 1-[(phenylmethyl)oxy]-4-(propyloxy)-2,3-naphthalenedicarboxylate*	Rt=3.98 $[MH]^+$436.98

Description 13

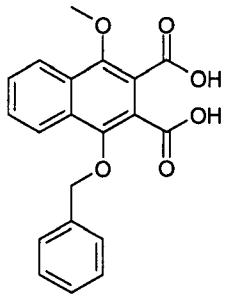
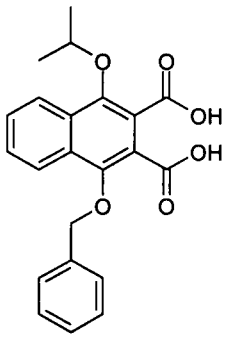
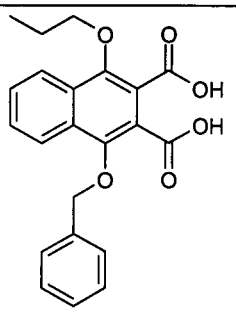
1-(Ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid



A mixture of diethyl 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylate (3.05g, 7.23mmol), ethanol (30ml), and 2N aqueous sodium hydroxide solution (35ml) was refluxed for 3 hours. The reaction mixture was cooled and evaporated. This was acidified with HCl (2N) and extracted with ethyl acetate twice. Combined organics were dried over magnesium sulphate

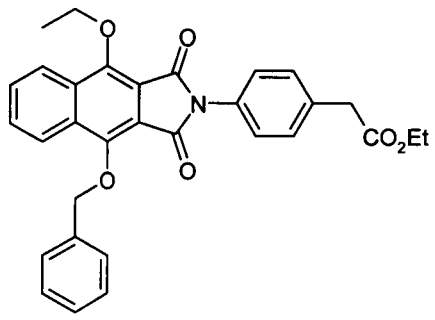
and the solvent evaporated to give the title compound as a white solid (2.55g, 6.97mmol). LC/MS: Rt=2.76, $[MH]^-$ 365.

The following compounds were prepared in a similar manner to 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid using the appropriate starting materials.

	Name	LC/MS
	*1-(Methyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid*	Rt=2.62 $[MH]^-$ 351
	*1-[Methylethoxy]-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid*	Rt=2.87 $[MH]^+$ 381
	*1-[(Phenylmethyl)oxy]-4-(propyloxy)-2,3-naphthalenedicarboxylic acid*	Rt=2.95 $[MH]^-$ 379

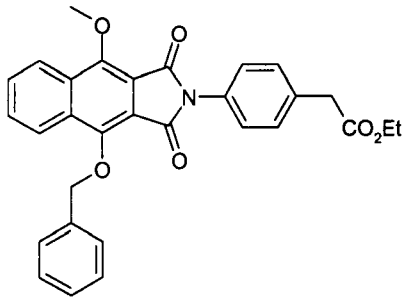
Description 14

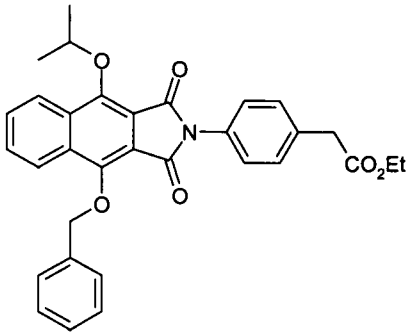
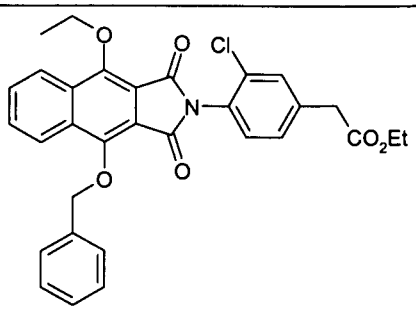
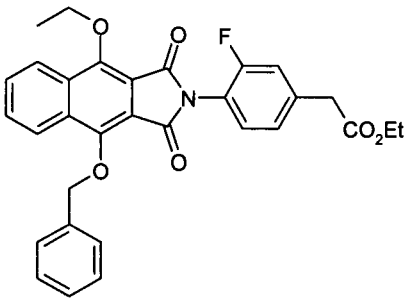
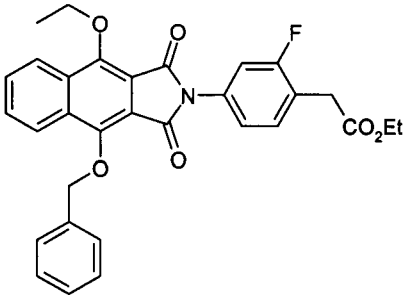
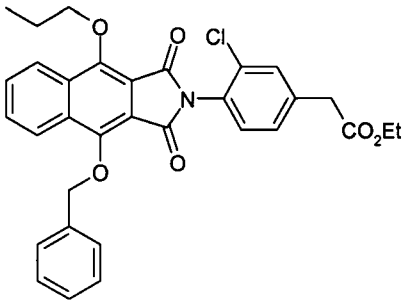
Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2- yl}phenyl)acetate

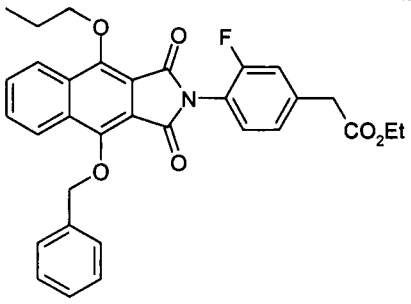
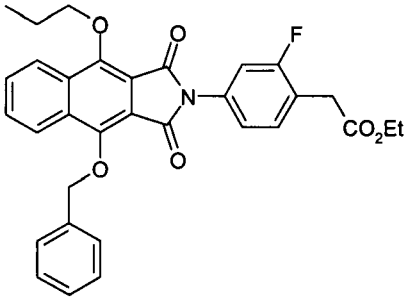
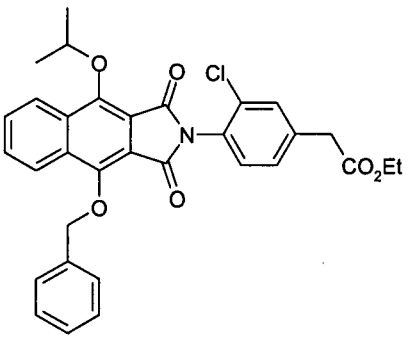
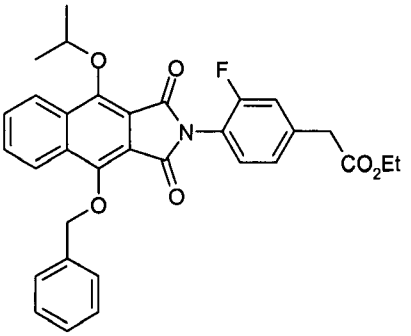
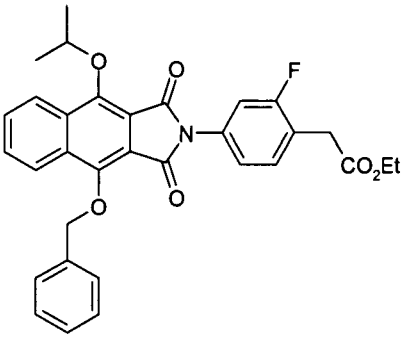


A mixture of 1-(ethyloxy)-4-[(phenylmethyl)oxy]-2,3-naphthalenedicarboxylic acid (2.55g, 6.97mmol) and ethyl (4-aminophenyl)acetate (2.49g, 13.9mmol) were heated to 120°C in acetic acid (20ml) for 18 hours. The reaction mixture was diluted with brine and extracted with ethyl acetate twice. Combined organics were washed with water then dried over magnesium sulphate, the solvent evaporated to give a brown oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as a peach coloured solid (2.63g, 5.17mmol). LC/MS: Rt=3.95, $[MH]^+$ 510.

The following compounds were 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 using the appropriate starting materials and on some occasions, MDAP was included (denoted by *).

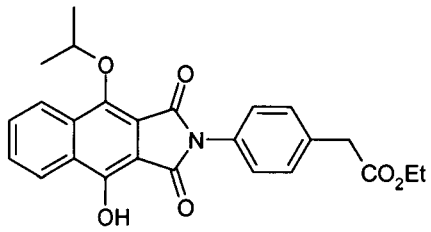
	Name	LC/MS
	*Ethyl (4-{4-(methyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.94 $[MH]^+$496

	*Ethyl (4-{4-[(methylethoxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.96 $[MH]^+$ 524
	*Ethyl (3-chloro-4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate**	Rt=4.04 $[MH]^+$ 544
	*Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate**	Rt=3.95 $[MH]^+$ 528
	*Ethyl (4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate**	Rt=3.96 $[MH]^+$ 528
	*Ethyl {3-chloro-4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=4.07 $[MH]^+$ 558

	*Ethyl {4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=4.11 $[MH]^+$ 542
	*Ethyl {4-[1,3-dioxo-4-[(phenylmethyl)oxy]-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=4.13 $[MH]^+$ 542
	*Ethyl (3-chloro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate**	Rt=4.13 $[MH]^+$ 558
	*Ethyl (3-fluoro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate**	Rt=3.98 $[MH]^+$ 542
	*Ethyl (2-fluoro-4-{4-[(1-methylethyl)oxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate**	Rt=4.01 $[MH]^+$ 542

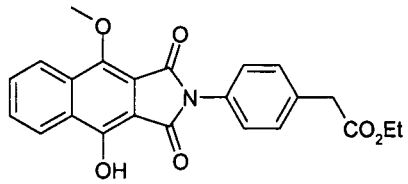
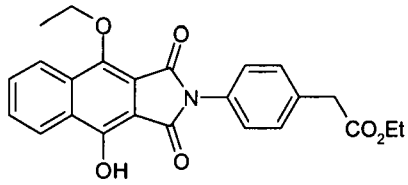
Description 15

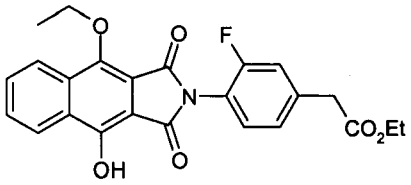
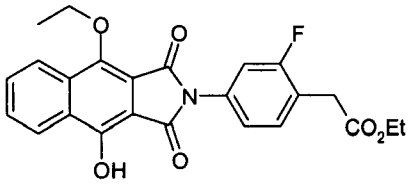
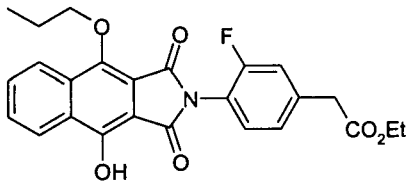
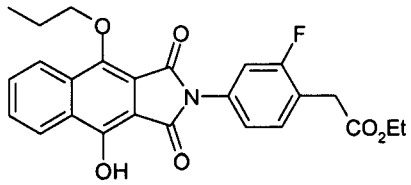
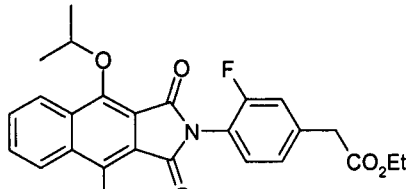
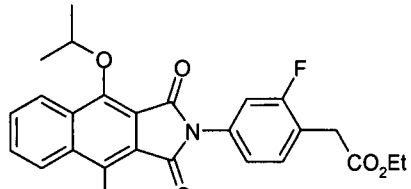
Ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate



10% Palladium on carbon (0.365g) was suspended in ethanol (500ml), to this was added ethyl (4-{4-[methylethoxy]-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (3.65g, 6.98mmol). The reaction was stirred at room temperature under an atmosphere of hydrogen for 3 hours. This was filtered through a bed of celite under a blanket of argon, and washed with ethanol and dichloromethane. The filtrate was evaporated to give an orange solid (3.05g, 7.04mmol). LC/MS: Rt=3.72, $[MH]^+$ 434.

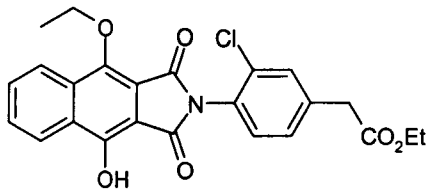
The following compounds were prepared in a similar manner to ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate using the appropriate starting materials.

	Name	LC/MS
	*Ethyl {4-[4-hydroxy-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.51 $[MH]^+$406
	*Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.56 $[MH]^+$ 420

	*Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.50 $[MH]^+$ 437.99
	*Ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.63 $[MH]^+$ 438
	*Ethyl {3-fluoro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.76 $[MH]^-$ 450
	*Ethyl {2-fluoro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.81 $[MH]^-$ 450
	*Ethyl (3-fluoro-4-{4-hydroxy-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.69 $[MH]^-$ 450
	*Ethyl (2-fluoro-4-{4-hydroxy-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.74 $[MH]^+$ 452

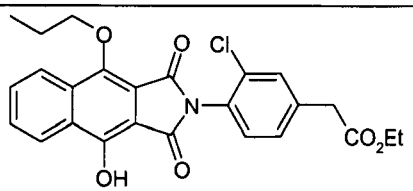
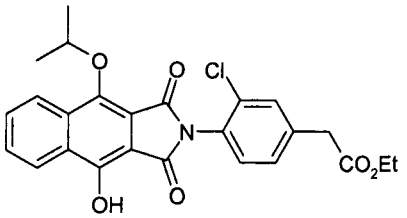
Description 16

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



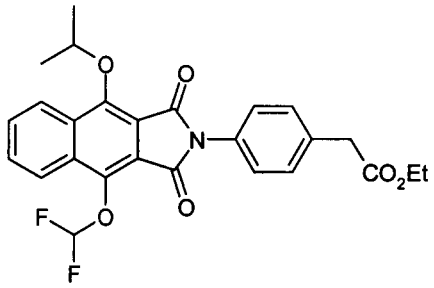
To a solution of ethyl (3-chloro-4-{4-(ethyloxy)-1,3-dioxo-9-[(phenylmethyl)oxy]-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (1.75g, 3.22mmol) in DCM (40ml), cooled to -78°C under an atmosphere of argon, was added boron tribromide (0.31ml, 3.22mmol) drop wise. Stirred at -78°C for 12 minutes. A further addition of boron tribromide (0.31ml, 3.22mmol) was made drop wise. The reaction mixture was quenched with water and warmed to room temperature. This was extracted twice with DCM using a hydrophobic frit. The organic phase was evaporated to an yellow solid. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-60%) in hexane to give the title compound as a orange oily solid (0.920g, 2.03mmol). LC/MS: Rt=3.65, $[MH]^+$ 454.

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

	Name	LC/MS
	*Ethyl {3-chloro-4-[4-hydroxy-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.80 $[MH]^+$ 468
	*Ethyl (3-chloro-4-{4-hydroxy-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.77 $[MH]^+$ 468

Description 17

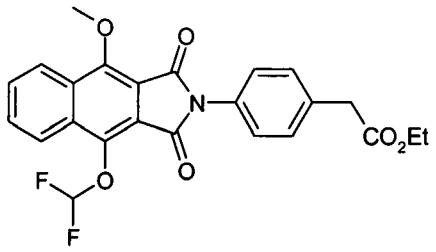
Ethyl (4-{4-[(difluoromethyl)oxy]-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2- yl}phenyl)acetate



To a solution of ethyl (4-{4-hydroxy-9-[methylethoxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (0.25g, 0.577mmols) in dimethylformamide (10ml), was added potassium carbonate (0.120g, 0.866mmol) followed by potassium iodide (0.048g, 0.289mmol). Chloro(difluoro)methane was bubbled through the solution at 80°C for 2 hours. Bubbling was ceased and heating continued for 25 hours. The cooled mixture was partitioned between 2x ethyl acetate and brine, the combined organics were washed with water, dried over sodium sulphate and evaporated down to a yellow oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane to give the title compound as a white coloured solid (0.142g, 0.294mmol). LC/MS: Rt=3.82, $[MH]^+$ 484.

Description 18

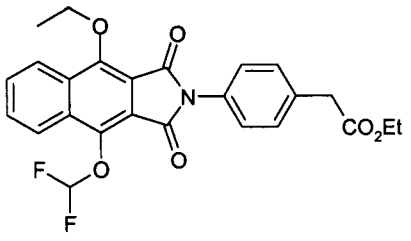
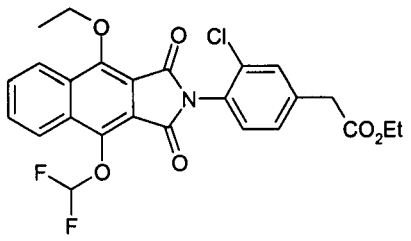
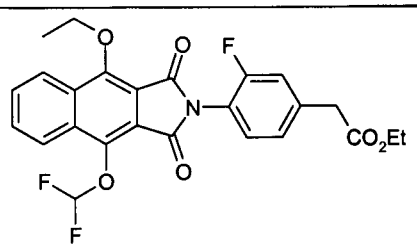
Ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate

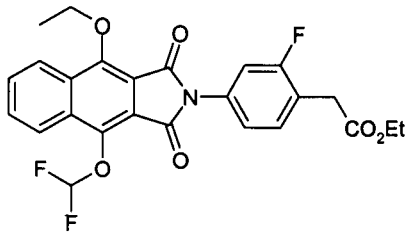
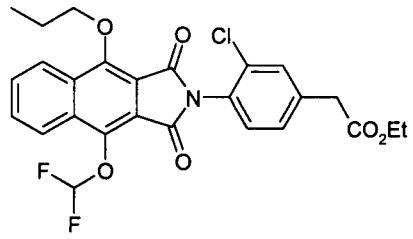
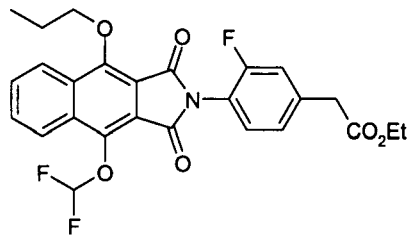
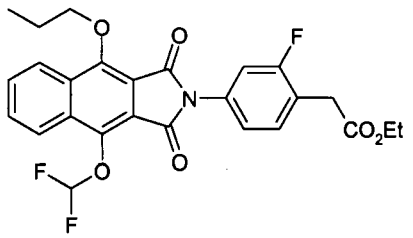
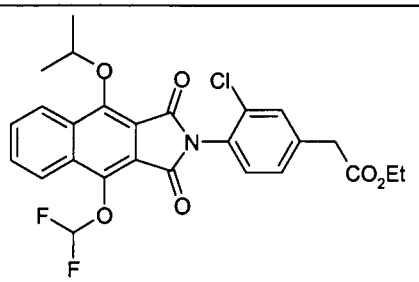
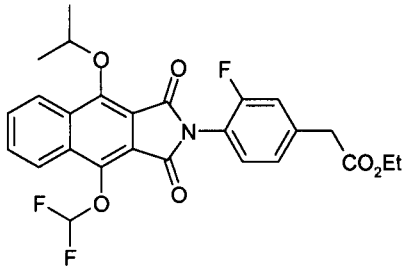


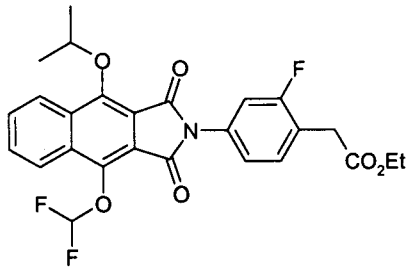
To a solution of ethyl {4-[4-hydroxy-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (0.700g, 1.73mmol) in dimethylformamide

(25ml) was added sodium carbonate (0.220g, 2.07mmol) followed by sodium chlorodifluoroacetate (0.315g, 2.07mmol). The mixture was heated to 100°C for 1.5 hours. Further sodium carbonate (0.220g, 2.07mmol) and sodium chlorodifluoroacetate (0.315g, 2.07mmol) was added, heating continued for 2 hours, and the same amounts added again. The mixture was cooled to room temperature and water added. The resulting beige solid was collected by filtration and washed with water. This was dried under vacuum (0.680g, 1.49mmol). LC/MS: Rt=3.62, $[MH]^+$ 456.

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

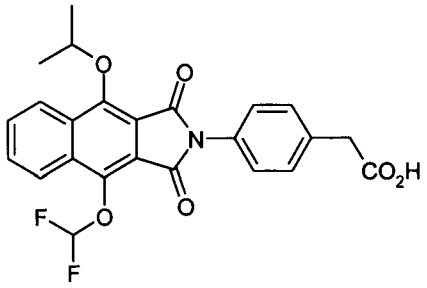
	Name	LC/MS
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.77 $[MH]^+$470
	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.69 $[MH]^+$503.89
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.73 $[MH]^+$488

	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.62 $[MH]^+$488
	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.86 $[MH]^-$ 516
	*Ethyl {4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.83 $[MH]^+$502
	*Ethyl {4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.85 $[MH]^+$502
	*Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.84 $[MH]^-$516
	*Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.76 $[MH]^+$502

	*Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*	Rt=3.75 $[MH]^+$502

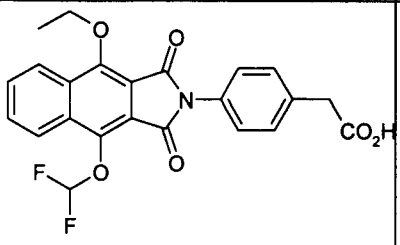
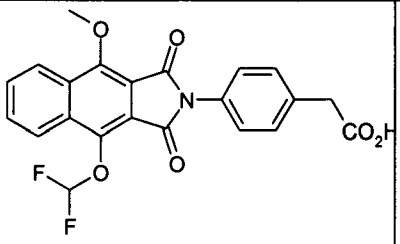
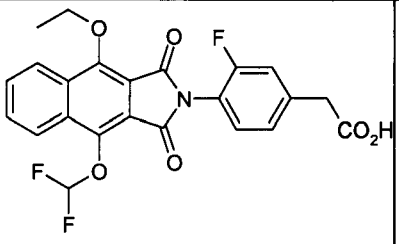
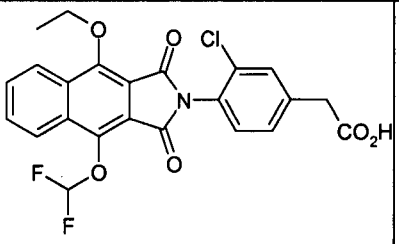
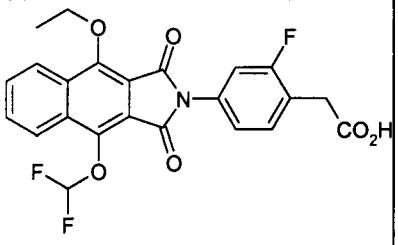
Example 8

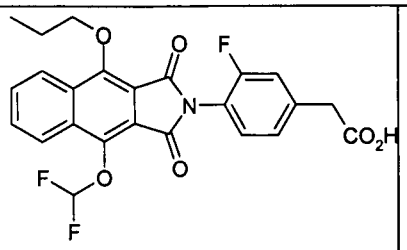
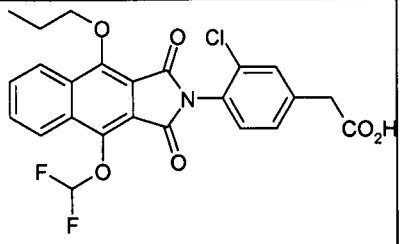
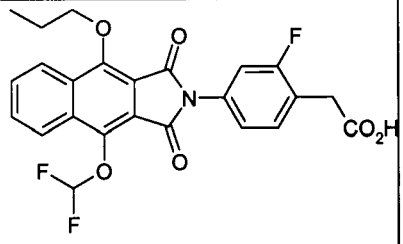
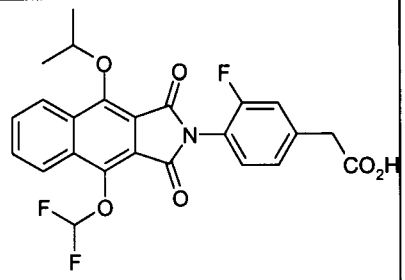
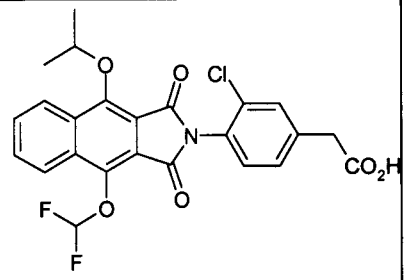
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid

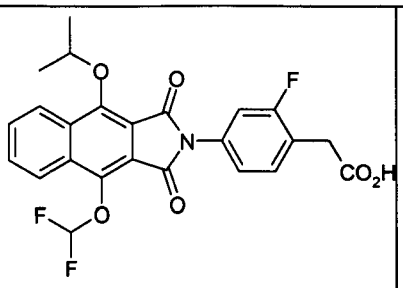


Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetate (0.14g, 0.289mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (8ml) for 1 hour. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration and washed with water. This was dried in the vacuum oven to give the title compound (0.120g, 0.026mmol). LC/MS: Rt=3.36, $[MH]^+$ 456.

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

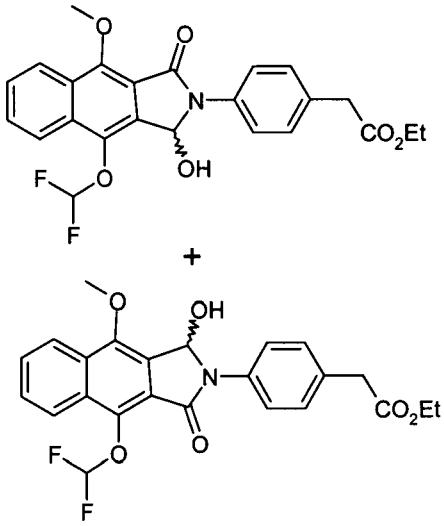
		Name	LC/MS
Example 9		*{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.29 $[MH]^+$442
Example 10		*{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.14 $[MH]^+$428
Example 11		*{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.33 $[MH]^+$460
Example 12		*{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.33 $[MH]^+$476
Example 13		*{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid*	Rt=3.25 $[MH]^+$460

Example 14		*{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.39 $[MH]^+$474
Example 15		*{3-chloro-4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.51 $[MH]^+$490
Example 16		*{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid*	Rt=3.41 $[MH]^+$474
Example 17		*(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid*	Rt=3.34 $[MH]^+$474
Example 18		*(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid*	Rt=3.41 $[MH]^+$490

Example 19		*(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid*	Rt=3.36 $[MH]^+$474

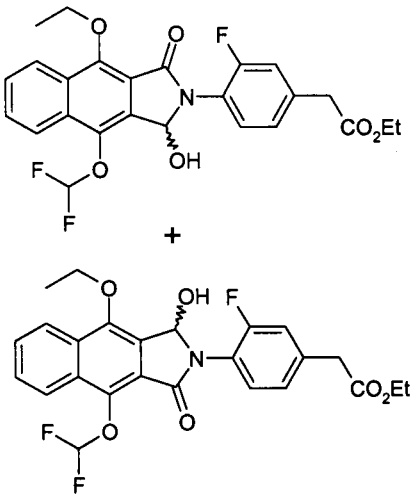
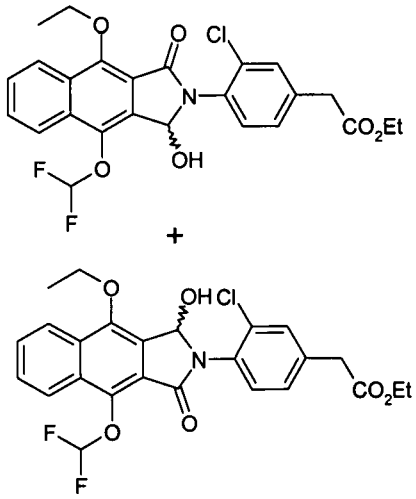
Description 19

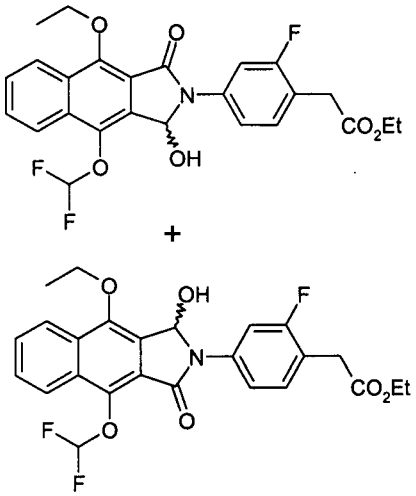
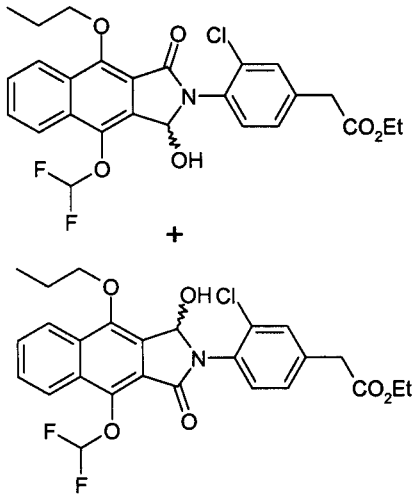
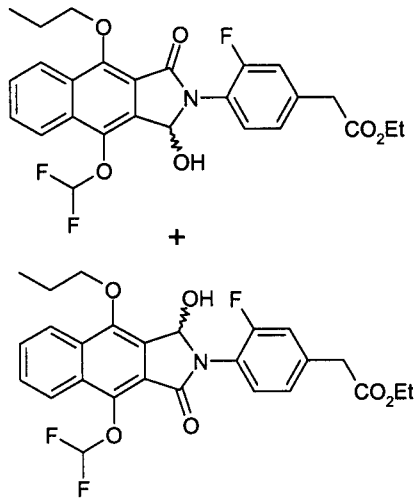
Ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate and Ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate

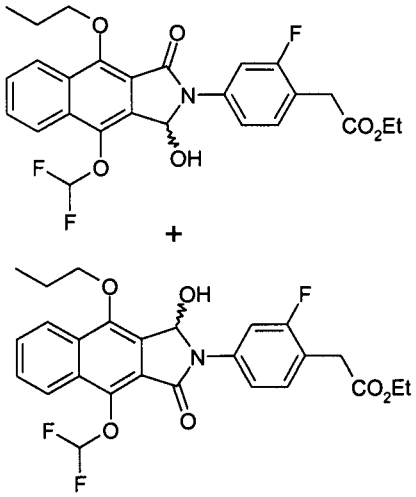
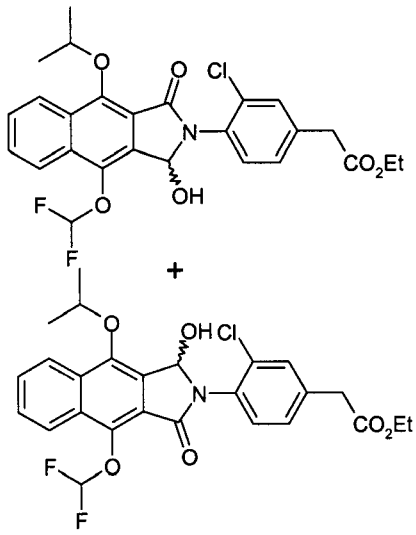
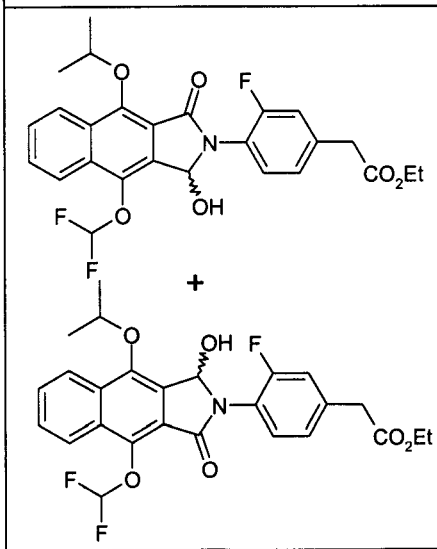


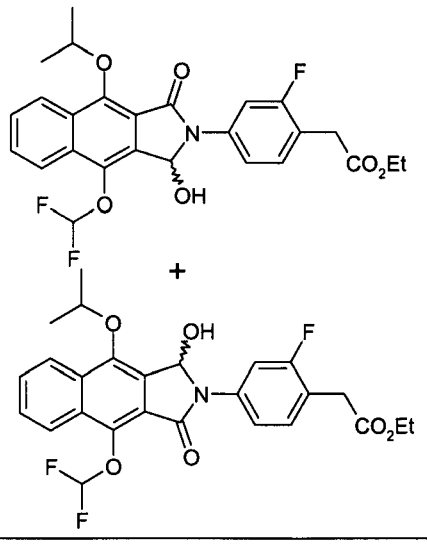
To a solution of ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (0.455g, 1.00mmol) in ethanol (4ml) and tetrahydrofuran (8ml), was added sodium borohydride (0.114g, 3.0mmol) portion wise. The reaction was stirred for 1 hour then a further portion of sodium borohydride (0.114g, 3.0mmol) was added, stirring continued at room temperature for 1 hour. The mixture was quenched with aqueous saturated ammonium chloride solution and then evaporated. This was extracted with ethyl acetate twice, dried over magnesium sulphate and evaporated to give the crude product (0.515g, 1.13mmol). LC/MS: Rt=3.21 & 3.26, $[MH]^+$457.97.

The following compounds were prepared in a similar manner to ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate and ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate using the appropriate starting materials.

	Name	LC/MS
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate* *Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.35, 3.38 $[MH]^+$490
	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate* *Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.43, 3.47 $[MH]^+$506

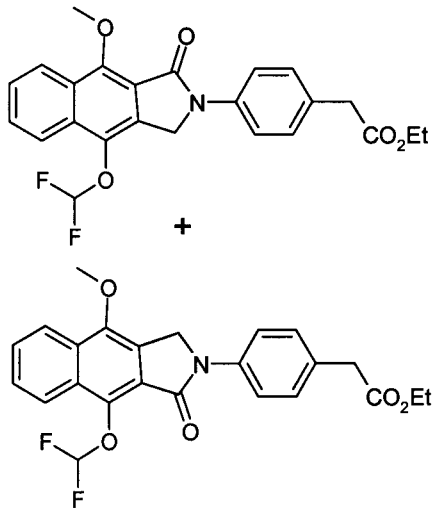
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate* *Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-3-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.43 $[MH]^+$490
	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate* *Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.60 $[MH]^+$520
	*Ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate –* *Ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.52 $[MH]^+$504

	*Ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-3-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate –* *Ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.64 $[MH]^+$504
	*Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate* *Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.53 $[MH]^+$520
	*Ethyl (4-{4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate* *Ethyl (4-{4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.44 $[MH]^+$504

	*Ethyl (4-{4-[(difluoromethyl)oxy]-1-hydroxy-9-[(1-methylethyl)oxy]-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate* *Ethyl (4-{4-[(difluoromethyl)oxy]-3-hydroxy-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate)*	Rt=3.57 $[MH]^+$504

Description 20

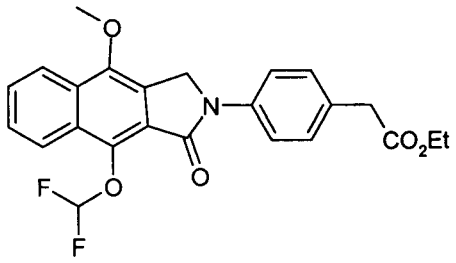
Ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate and ethyl {4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate



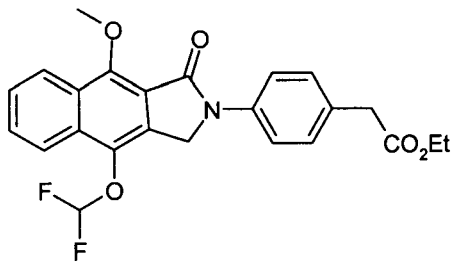
To a solution of ethyl {4-[4-[(difluoromethyl)oxy]-3-hydroxy-9-(methyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate and ethyl {4-[4-[(difluoromethyl)oxy]-1-hydroxy-9-(methyloxy)-3-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (0.457g, 1.00mmol) in trifluoroacetic acid (5ml) cooled to 0°C, was added triethylsilane (0.089ml, 0.561mmol). Stirring continued at 0°C for 15 minutes, and then the mixture was evaporated. The

crude mixture was purified using chromatography on silica gel, eluting with ethyl acetate (0-30%) in hexane. The isomers were then separated using super critical fluid chromatography.

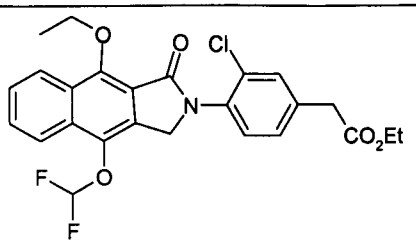
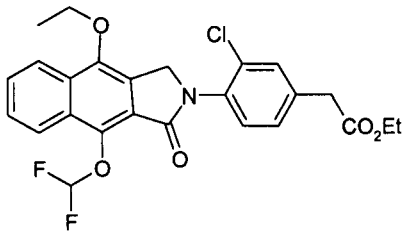
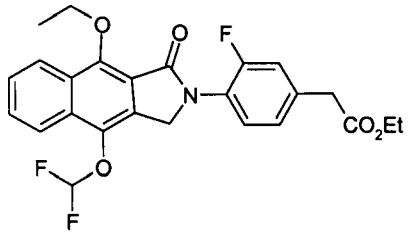
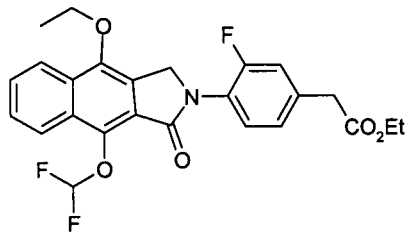
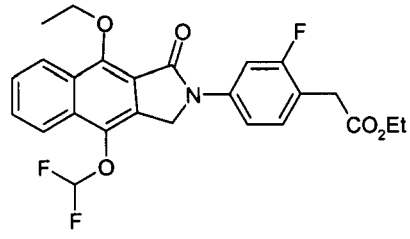
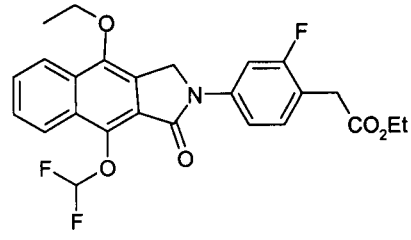
Ethyl {4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (0.036g, 0.082mmol). LC/MS: Rt=3.75, $[MH]^+$442

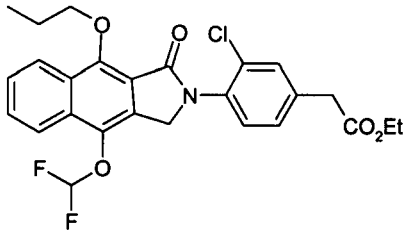
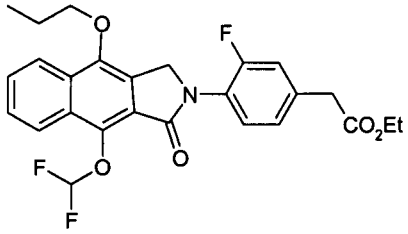
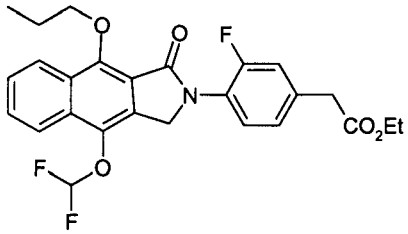
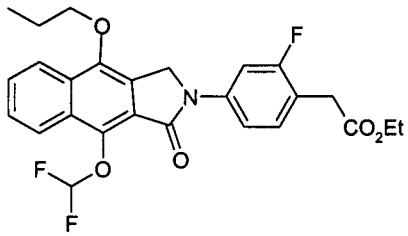
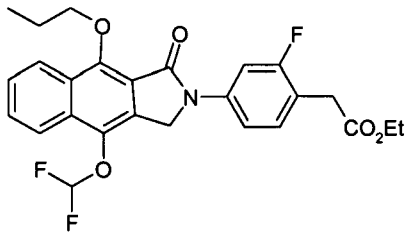
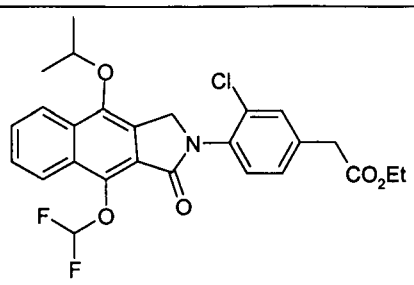


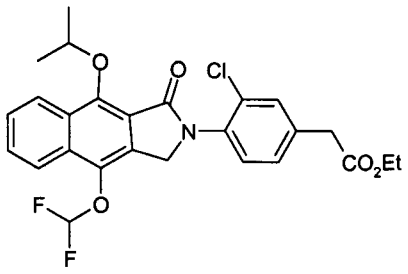
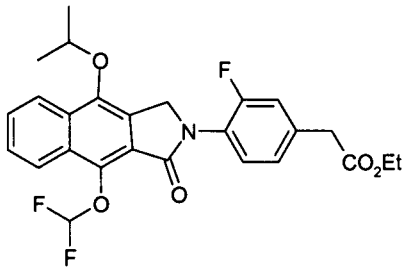
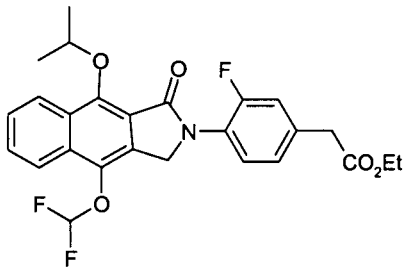
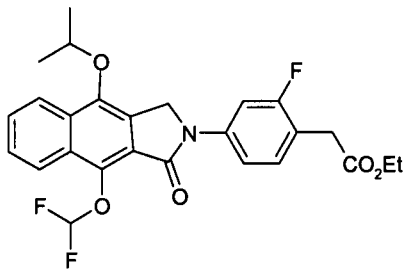
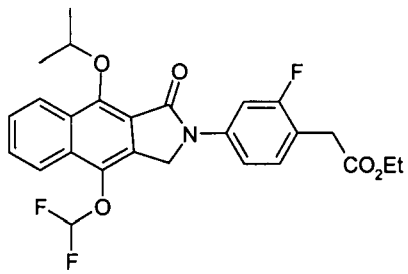
Ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate (0.036g, 0.082mmol). LC/MS: Rt=3.60, $[MH]^+$442



The following compounds were prepared in a similar manner to ethyl {4-[4-[(difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate and ethyl {4-[9-[(difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate using the appropriate starting materials and the isomers separated using high performance liquid chromatography or super critical fluid chromatography.

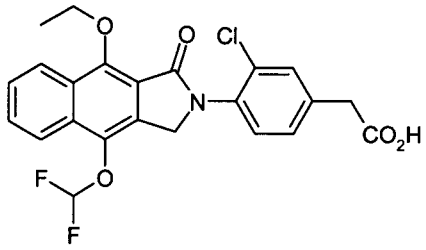
	Name	LC/MS
	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.69 $[MH]^+$490
	*Ethyl {3-chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.75 $[MH]^+$490
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.60 $[MH]^+$474
	*Ethyl {4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.65 $[MH]^+$474
	*Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.70 $[MH]^+$474
	*Ethyl {4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.73 $[MH]^+$474

	*Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetate*	Rt=3.83 $[MH]^+$504
	*Ethyl {4-[9-[(difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.89 $[MH]^+$488
	*Ethyl {4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate*	Rt=3.84 $[MH]^+$488
	*Ethyl {4-[9-[(difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.93 $[MH]^+$488
	*Ethyl {4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetate*	Rt=3.93 $[MH]^+$488
	*Ethyl (3-chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.81 $[MH]^+$504

	*Ethyl (3-chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetate*	Rt=3.76 $[MH]^+$504
	*Ethyl (4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.77 $[MH]^+$488
	*Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetate*	Rt=3.73 $[MH]^+$488
	*Ethyl (4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*	Rt=3.88 $[MH]^+$488
	*Ethyl (4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetate*	Rt=3.91 $[MH]^+$488

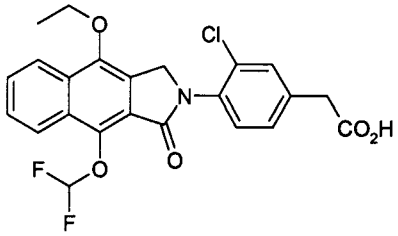
Example 20

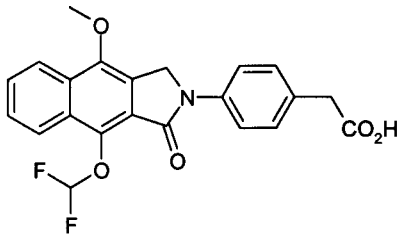
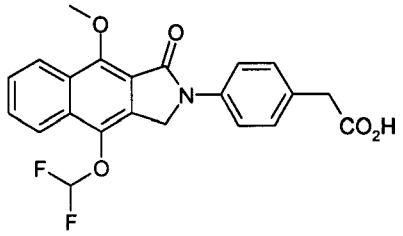
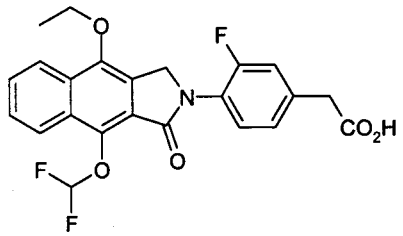
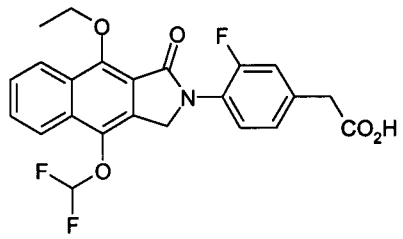
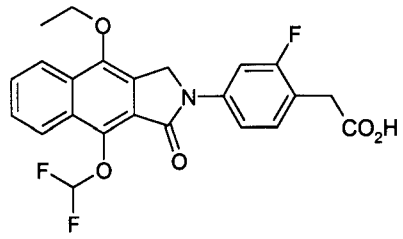
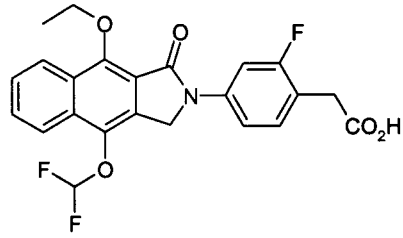
{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid

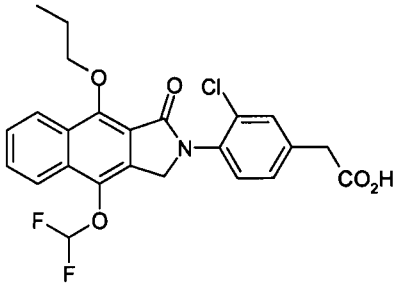
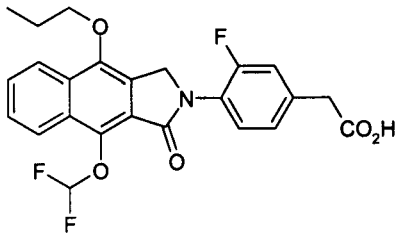
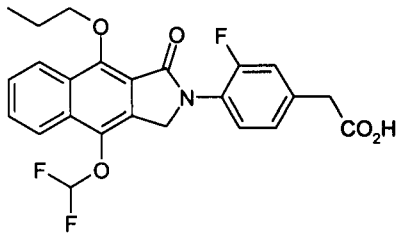
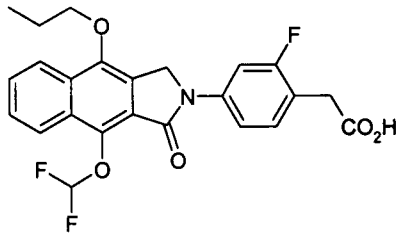
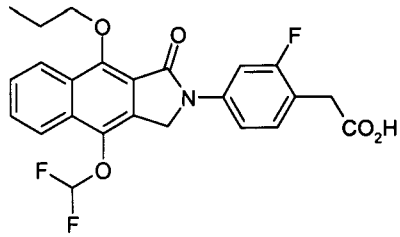
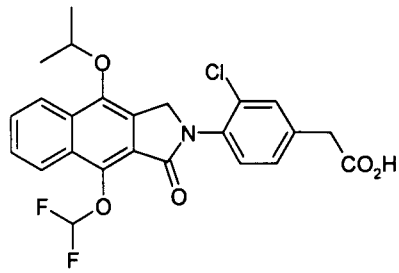


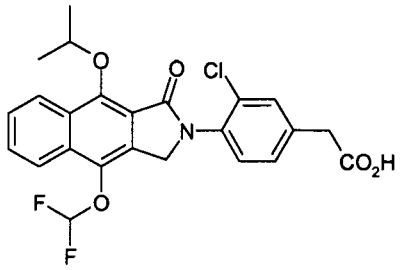
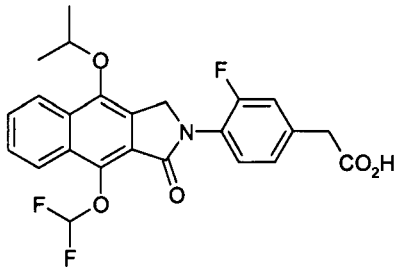
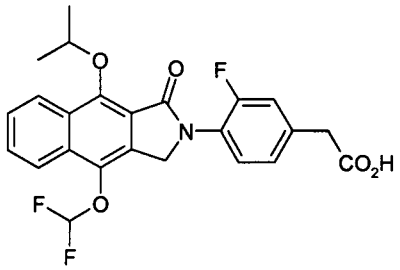
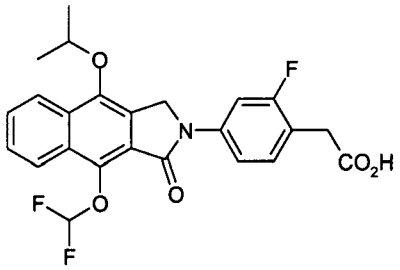
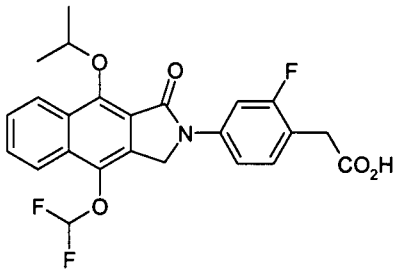
Ethyl {3-chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetate (0.141g, 0.288mmol) was heated to reflux in a 1:1 mixture of 2N sodium hydroxide : ethanol (6ml) for 1.5 hours. The reaction was cooled to room temperature. The ethanol was evaporated and the mixture acidified with 2N aqueous hydrochloric acid. The resulting white solid was collected by filtration, washed with water and dried under vacuum to give the title compound (0.125g, 0.271mmol). LC/MS: Rt=3.19, $[MH]^+$ 462.

The following compounds were prepared in a similar manner to {3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetic acid using the appropriate starting materials. Some compounds underwent an alternative aqueous work-up with ethyl acetate extraction followed by purification by MDAP (denoted by *), or were purified by trituration with diethyl ether (denoted by #).

		Name	LC/MS
Example 21		*{3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.28 $[MH]^+$462

Example 22		*{4-[9-[(Difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.16 $[MH]^+$ 414
Example 23		*{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid*	Rt=3.11 $[MH]^+$414
Example 24		*{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.20 $[MH]^+$446
Example 25		*{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.10 $[MH]^+$446
Example 26		*{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid**	Rt=3.31 $[MH]^+$446
Example 27		*{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid#*	Rt=3.28 $[MH]^+$ 446

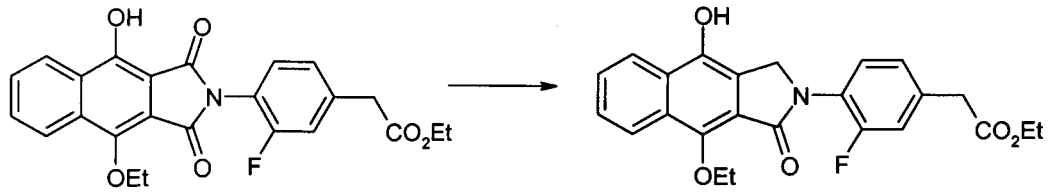
Example 28		*{3-Chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid**	Rt=3.38 $[MH]^+$476
Example 29		*{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid**	Rt=3.42 $[MH]^+$460
Example 30		*{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid*	Rt=3.32 $[MH]^+$460
Example 31		*{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid*	Rt=3.51 $[MH]^+$460
Example 32		*{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid**	Rt=3.46 $[MH]^+$460
Example 33		*(3-Chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid**	Rt=3.39 $[MH]^+$476

Example 34		*(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid**	Rt=3.32 $[MH]^+$476
Example 35		*(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid**	Rt=3.32 $[MH]^+$460
Example 36		*(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid**	Rt=3.36 $[MH]^+$460
Example 37		*(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid**	Rt=3.44 $[MH]^+$460
Example 38		*(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid**	Rt=3.41 $[MH]^+$460

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid [Example 25] has also been conveniently prepared using a regioselective methodology as follows:

Description 21

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

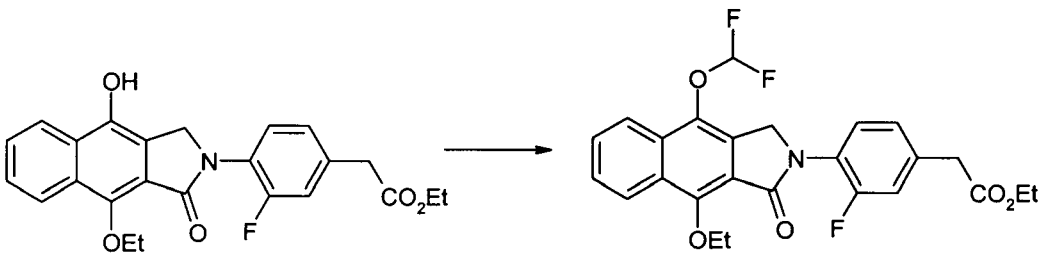


To a solution of ethyl {4-[4-(ethyloxy)-9-hydroxy-1,3-dioxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetate (2.50g, 5.72mmol) in THF (50ml) under an argon atmosphere, was added sodium borohydride (0.217g, 5.72mmol) followed by borane THF complex solution (1.0M in THF, 5.72ml, 5.72mmol). This was stirred at room temperature for 2 hours. A further 5.72mmol of sodium borohydride and borane THF complex was added to the reaction mixture and stirring continued for 2 hours. Finally, a further 2.86mmol addition of sodium borohydride and borane THF complex was made and stirring continued for 1.5 hours until the reaction was complete. This was quenched with ethyl acetate (100ml) and methanol (3ml) then washed with 2N HCl (100ml). The aqueous was re-extracted with ethyl acetate (200ml). The combined organics were washed with brine (200ml), dried over magnesium sulphate, filtered and evaporated to give the title compound as a pale yellow solid (2.45g, 5.79mmol).

LC/MS: Rt=3.04, $[MH]^+$ 424.

Description 22

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

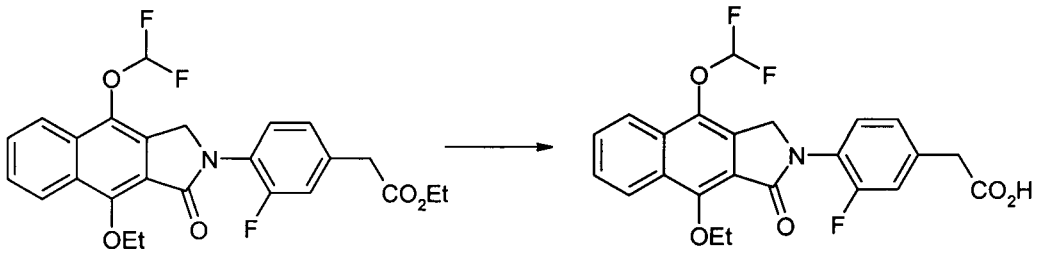


To a solution of ethyl {4-[9-(ethyloxy)-4-hydroxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetate (2.40g, 5.67mmols) in DMF (30ml) was added sodium chlorodifluoroacetate (1.72g, 11.34mmol) and sodium carbonate (1.20g, 11.34mmol). The mixture was heated to 100°C for 3 hours. Further sodium chlorodifluoroacetate (1.72g, 11.34mmol) was added, heating continued for 1.5 hours, and the same amount added again and heating continued for 30 minutes. The mixture was cooled to room temperature and partitioned between ethyl acetate x2 and water. The combined organics were washed with water x3 and brine. This was dried over magnesium sulphate, filtered and evaporated to a brown oil. This was purified by chromatography on silica gel, eluting with ethyl acetate (5-40%) in hexane to give the title compound as a yellow solid (0.60g, 1.27mmol).

LC/MS: Rt=3.49, $[MH]^+$ 474.

Example 25

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



Ethyl {4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetate (0.60g, 1.27mmol) was heated to 100°C in a 1:1 mixture of acetic acid : 2N aqueous hydrochloric acid (20ml) for 50 minutes. The reaction was cooled to room temperature. On addition of water, the resulting white solid was collected by filtration, washed with water and dried under vacuum to give the title compound (0.516g, 1.09mmol).

LC/MS: Rt=3.13, $[MH]^+$ 446.

^{1}H-NMR (DMSO) δ8.42 (1H, ddd, J=8.4,1.1,0.6Hz), δ8.12 (1H, d, J=8.5Hz), δ7.84 (1H, ddd, J=8.2,6.9,1.3Hz), δ7.74 (1H, ddd, J=8.4, 6.8, 1.2Hz), δ7.63 (1H, t, J=8.1Hz), δ 7.32 (1H, dd, 11.5,1.9Hz), δ7.22 (1H, dd, 8.1,1.8Hz), δ7.30 (1H, t, 73.6Hz), δ5.06 (2H, s), δ 4.50 (2H, q, J=7.0Hz), δ3.67 (2H, s), δ1.44 (3H, t, 7.0Hz).

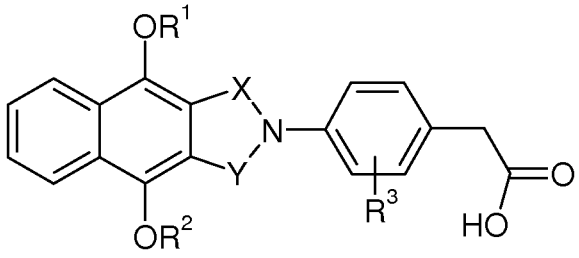
Biological data

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 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 50ul 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 pEC_{50} values of 6.1 or higher. Certain examples exhibited pEC_{50} values of 7 or higher and intrinsic activities of 50% or higher.

Claims

1. A compound of formula (I) or a pharmaceutically acceptable derivative thereof,



(I)

wherein,

R^1 and R^2 independently represent C_{1-4} alkyl or difluoromethyl provided that at least one of R^1 and R^2 represents difluoromethyl;

R^3 represents H, F, Cl or Br; and

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

2. A compound of formula (I), according to clam 1, wherein one of R^1 and R^2 represents C_{1-4} alkyl and the other represents difluoromethyl.

3. A compound of formula (I), according to clam 1, wherein both R^1 and R^2 represent difluoromethyl.

4. A compound of formula (I), according to any of claims 1 to 3, wherein both X and Y represent C=O.

5. A compound of formula (I), according to any of claims 1 to 4, wherein R^3 represents H, F or Cl.

6. A compound of formula (I), according to claim 1, selected from the group consisting of:
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-chlorophenyl)acetic acid;
(4-{4,9-Bis[(difluoromethyl)oxy]-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;
{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;
{3-Chloro-4-[4-[(difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-1,3-dioxo-9-(propyloxy)-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-2-fluorophenyl}acetic acid;

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-3-fluorophenyl)acetic acid;

(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}phenyl)acetic acid;

(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl}-2-fluorophenyl)acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{3-Chloro-4-[9-[(difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(methyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]phenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-4-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;

4-[4-[(Difluoromethyl)oxy]-9-(ethyloxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;

{3-Chloro-4-[4-[(difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]phenyl}acetic acid;

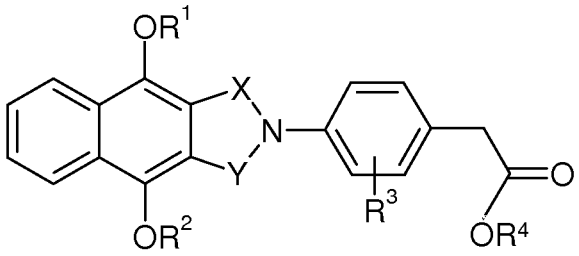
{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-fluorophenyl}acetic acid;

{4-[9-[(Difluoromethyl)oxy]-1-oxo-4-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;

{4-[4-[(Difluoromethyl)oxy]-1-oxo-9-(propyloxy)-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-2-fluorophenyl}acetic acid;
(3-Chloro-4-{9-[(difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetic acid;
(3-Chloro-4-{4-[(difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}phenyl)acetic acid;
(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-3-fluorophenyl)acetic acid;
(4-{9-[(Difluoromethyl)oxy]-4-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-2-fluorophenyl)acetic acid;
(4-{4-[(Difluoromethyl)oxy]-9-[(1-methylethyl)oxy]-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl}-2-fluorophenyl)acetic acid; or a pharmaceutically acceptable derivative thereof.

7. A process for preparing a compound of formula (I), according to claim 1, wherein one of X and Y represents C=O and the other represents CH_2, and R^1, R^2 and R^3 are as defined in claim 1, which process comprises reacting a compound of formula (II),

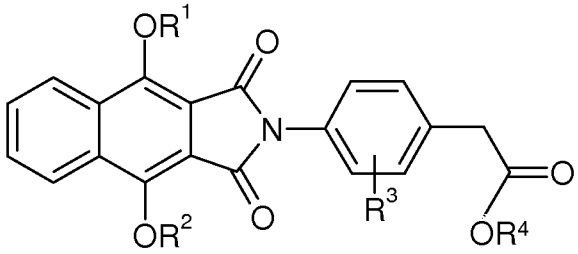


(II)

wherein, one of X and Y represents C=O and the other represents CH_2; R^1, R^2 and R^3 are as hereinbefore defined in claim 1; and R^4 represents

C_{1-6} alkyl; with a suitable base and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

8. A process for preparing a compound of formula (I), according to claim 1, wherein X and Y represent C=O and R^1, R^2 and R^3 are as defined in claim 1, which process comprises adding a compound of formula (III),



(III)

wherein, R^1, R^2 and R^3 are as defined in claim 1; and R^4 represents C_{1-6} alkyl; to a suitable acid or mixture of acids, and optionally thereafter forming a pharmaceutically acceptable derivative of the compound so formed, and/or converting one compound of formula (I) to another.

9. A compound of formula (I), according to claim 1, for use in human or veterinary medicine.

10. A compound of formula (I), according to claim 1, 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.

11. 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), according to claim 1.

12. Use of a compound of formula (I), according to claim 1, 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.

13. A pharmaceutical composition comprising a compound of formula (I), according to claim 1, and one or more acceptable carriers or diluents therefor.

14. A pharmaceutical composition according to claim 13, comprising one or more additional therapeutic agents.