

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
2 October 2008 (02.10.2008)

PCT

(10) International Publication Number
WO 2008/116304 A1

(51) International Patent Classification:

C07D 209/64 (2006.01) *A61K 31/4745* (2006.01)
A61K 31/4035 (2006.01) *C07D 471/04* (2006.01)

(21) International Application Number:

PCT/CA2008/000561

(22) International Filing Date: 25 March 2008 (25.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/920,018 26 March 2007 (26.03.2007) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BI, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report

WO 2008/116304 A1

(54) Title: NAPHTHALENE AND QUINOLINE SULFONYLUREA DERIVATIVES AS EP4 RECEPTOR ANTAGONISTS

(57) Abstract: The invention is directed to naphthalene and quinoline sulfonylurea derivatives as EP4 receptor antagonists useful for the treatment of EP4 mediated diseases or conditions, such as acute and chronic pain, osteoarthritis, rheumatoid arthritis and cancer. Pharmaceutical compositions and methods of use are also included.

TITLE OF THE INVENTION

NAPHTHALENE AND QUINOLINE SULFONYLUREA DERIVATIVES AS EP4 RECEPTOR ANTAGONISTS.

5 BACKGROUND OF THE INVENTION

This invention relates to compounds and methods for treating prostaglandin E mediated diseases, and certain pharmaceutical compositions thereof. More particularly, the compounds of the invention are structurally different from NSAIDs and opiates, and are antagonists of the pain and inflammatory effects of E-type prostaglandins.

10 Three 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; *Journal of Lipid Mediators and Cell Signalling*, 1996, 14, 83-87; and *Prostaglandins and Other Lipid Mediators*, 2002, 69, 15 557-573.

20 Thus, selective prostaglandin ligands, agonists or antagonists, depending on which prostaglandin E receptor subtype is being considered, have anti-inflammatory, antipyretic and analgesic properties similar to a conventional non-steroidal anti-inflammatory drug, and in addition, have effects on vascular homeostasis, reproduction, gastrointestinal functions and bone metabolism. These compounds may have a diminished ability to induce some of the mechanism-based side effects of NSAIDs which are indiscriminate cyclooxygenase inhibitors. In particular, the compounds are believed to have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

25 In The Journal of Clinical Investigation (2002, 110, 651-658), studies suggest that chronic inflammation induced by collagen antibody injection in mice is mediated primarily through the EP4 subtype of PGE₂ receptors. Patent application publications WO 96/06822 (March 7, 1996), WO 96/11902 (April 25, 1996) and EP 752421-A1 (January 08, 1997) disclose compounds as being useful in the treatment of prostaglandin mediated diseases.

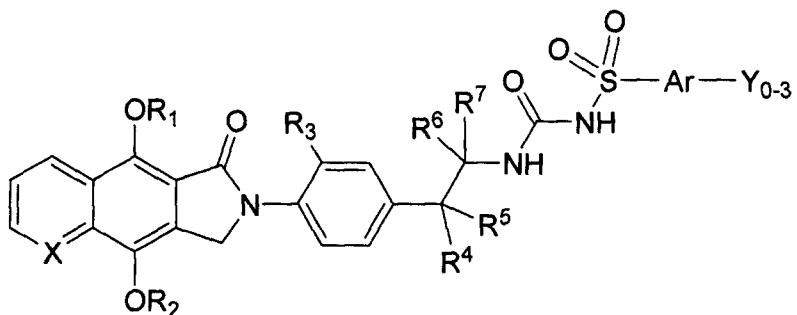
30 The present invention is directed to novel compounds that are antagonists of the EP4 subtype of PGE₂ receptors. The compounds would therefore be useful for the treatment of diseases or conditions mediated by the EP4 receptor, such as acute and chronic pain, osteoarthritis, rheumatoid arthritis and cancer.

SUMMARY OF THE INVENTION

The invention is directed to naphthalene and quinoline sulfonylurea derivatives as EP4 receptor antagonists useful for the treatment of EP4 mediated diseases or conditions, such as acute and chronic pain, osteoarthritis, rheumatoid arthritis and cancer. Pharmaceutical compositions and methods of use are also included.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses a genus of compounds of Formula I



10

I

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of N or CH;

15 R¹ and R² are independently selected from the group consisting of: C₁-6alkyl, C₃-6cycloalkyl, and C₁-6fluoroalkyl;

R³ is selected from the group consisting of: halogen, C₁-6alkyl and C₁-6haloalkyl;

20 R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of: hydrogen, halogen, C₁-6alkyl and C₃-6cycloalkyl; and R⁴ and R⁵ or R⁶ and R⁷ can join to make a 3-6 membered monocyclic cycloalkane ring;

Ar is selected from the group consisting of: C₃-6cycloalkyl, aryl, heteroaryl, and heterocyclyl, or 25 a fused analog of C₃-6cycloalkyl, aryl, heteroaryl, and heterocyclyl; and

each Y is independently selected from the group consisting of: halo, methyl, ethyl, methoxy, CF₃, CF₃O- and hydroxy.

Within the genus, the invention encompasses a sub-genus of compounds of Formula I wherein Ar is phenyl or naphthyl.

Within this sub-genus, the invention encompasses a class of compounds of Formula I wherein Ar is phenyl.

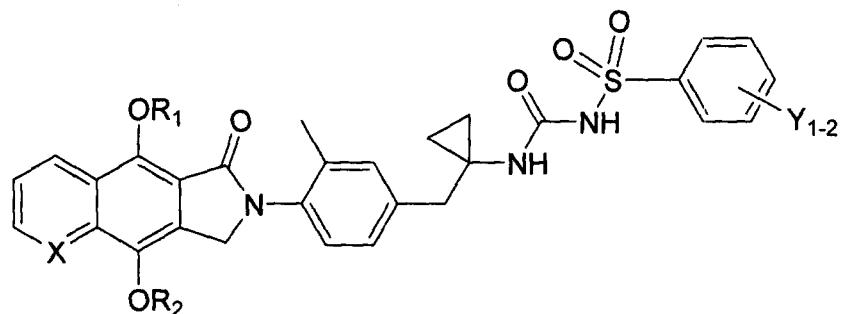
5 Also within the genus, the invention encompasses a sub-genus of compounds of Formula I wherein R³ is methyl.

Also within the genus, the invention encompasses a sub-genus of compounds of Formula I wherein: R⁴ and R⁵ are hydrogen and R⁶ and R⁷ are joined to make a cyclopropyl ring.

10 Also within the genus, the invention encompasses a sub-genus of compounds of Formula I wherein X is N.

Also within the genus, the invention encompasses a sub-genus of compounds of Formula I wherein X is CH.

15 Also within the genus, the invention encompasses a sub-genus of compounds according to Formula Ia



Ia

20 or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of N or CH;

25 R¹ and R² are the same and selected from the group consisting of: ethyl, 2,2,2-trifluoroethyl and difluoromethyl; and

one or two Y groups are present and each Y is independently selected from the group consisting of: F, Cl, Br, methyl, ethyl, methoxy, CF₃, CF₃O- and hydroxy.

Within this sub-genus the invention encompasses a class of compounds of Formula Ia wherein X is N.

Also within this sub-genus the invention encompasses a class of compounds of Formula Ia wherein X is CH.

5 The invention also encompasses a compound selected from the following group:

2,6-dichloro-*N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

10 *N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-methylbenzenesulfonamide;

2-chloro-*N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl] benzenesulfonamide;

15 *N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-methylbenzenesulfonamide;

20 *N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-methoxybenzenesulfonamide;

2-bromo-*N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

25 *N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-dimethoxybenzenesulfonamide;

30 *N*-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-(trifluoromethyl)benzenesulfonamide;

N-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]naphthalene-2-sulfonamide;

N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-bis(trifluoromethyl)benzenesulfonamide;

5 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-dimethylbenzenesulfonamide;

2,3-dichloro-*N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

10 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-fluorobenzenesulfonamide;

15 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-(trifluoromethoxy)benzenesulfonamide;

N-{[(2-{4-[4,9-bis(difluoromethoxy)-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl]-3-methylphenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

20 2-chloro-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide;

2-chloro-*N*-[({2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[*f*]isoindol-2-yl)-3-methylphenyl]-2,2-difluoroethyl}amino)carbonyl] benzenesulfonamide;

25 2-chloro-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4-*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}naphthalene-2-sulfonamide; and

30 2-methoxy-4-methyl-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4-*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide;

or a pharmaceutically acceptable salt of any of the foregoing compounds.

The invention also encompasses a compound which is the hydrochloride salt of 2-chloro-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide.

5 The invention also encompasses a pharmaceutical composition comprising a compound of Formula I in admixture with one or more physiologically acceptable carriers or excipients.

The invention also encompasses a compound of Formula I or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

10 The invention also encompasses a method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE2 at EP4 receptors, which method comprises administering to said subject an effective amount of a compound of Formula I.

15 The invention also encompasses the use of a compound of Formula I for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE2 at EP4 receptors.

20 The invention also encompasses a method for treating acute or chronic pain, migraine, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, gout, bursitis, ankylosing spondylitis, primary dysmenorrhea, cancer or atherosclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt thereof.

Abbreviations

The following abbreviations have the indicated meanings:

25	DCM	=	dichloromethane
	DME	=	dimethyl ether
	DMF	=	N,N-dimethylformamide
	DMS	=	dimethylsulfide
	RT	=	room temperature
30	TFA	=	trifluoroacetic acid
	THF	=	tetrahydrofuran
	TLC	=	thin layer chromatography

Definitions

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

5 "Fluoroalkyl" means alkyl as defined above wherein one or more hydrogen atoms have been replaced by fluoro atoms.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl 10 include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-but enyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

15 "Cycloalkyl" means mono- or bicyclic saturated carbocyclic rings, each of which having from 3 to 10 carbon atoms. A "fused analog" of cycloalkyl means a monocyclic rings fused to an aryl or heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl and fused analogs thereof include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl, and the 20 like.

"Alkoxy" means alkoxy groups of a straight or branched having the indicated number of carbon atoms. C₁-6alkoxy, for example, includes methoxy, ethoxy, propoxy, isopropoxy, and the like.

25 "Cycloalkoxy" means cycloalkyl as defined above bonded to an oxygen atom, such as cyclopropyloxy.

"Fluoroalkoxy" means alkoxy as defined above wherein one or more hydrogen atoms have been replaced by fluoro atoms.

30 "Aryl" means mono- or bicyclic aromatic rings containing only carbon atoms. A "fused analog" of aryl means an aryl group fused to a monocyclic cycloalkyl or monocyclic heterocycl group in which the point of attachment is on the aromatic portion. Examples of aryl and fused analogs thereof include phenyl, naphthyl, indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydrobenzofuranyl, dihydrobenzopyranyl, 1,4-benzodioxanyl, and the like.

35 "Heteroaryl" means a mono- or bicyclic aromatic ring containing at least one heteroatom selected from N, O and S, with each ring containing 5 to 6 atoms. A "fused analog" of heteroaryl means a heteroaryl group fused to a monocyclic cycloalkyl or monocyclic

heterocyclyl group in which the point of attachment is on the aromatic portion. Examples of heteroaryl include pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, 5 benzothiophenyl, furo(2,3-b)pyridyl, quinolyl, indolyl, isoquinolyl, and the like.

"Heterocyclyl" means mono- or bicyclic saturated rings or partially unsaturated monocyclic rings that are not aromatic containing at least one heteroatom selected from N, S and O, each of said rings having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. A "fused analog" of heterocyclyl means a monocyclic heterocycle fused to an aryl or 10 heteroaryl group in which the point of attachment is on the non-aromatic portion. Examples of "heterocyclyl" and fused analogs thereof include pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, 2,3-dihydrofuro(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolinyl, tetrahydroisoquinolinyl, dihydroindolyl, and the like. The term also includes partially 15 unsaturated monocyclic rings that are not aromatic, such as 2- or 4-pyridones attached through the nitrogen or N-substituted-(1H,3H)-pyrimidine-2,4-diones (N-substituted uracils).

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

"Haloalkyl" means alkyl as defined above wherein one or more hydrogen atoms have been replaced by halo atoms, also defined above.

20 Optical Isomers - Diastereomers - Geometric Isomers - Tautomers

Compounds of Formula I contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to comprehend all such isomeric forms of the compounds of Formula I.

25 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

Some of the compounds described herein may exist with different points of attachment of hydrogen, referred to as tautomers. Such an example may be a ketone and its enol 30 form known as keto-enol tautomers. The individual tautomers as well as mixture thereof are encompassed with compounds of Formula I.

Compounds of the Formula I may be separated into diastereoisomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example MeOH or EtOAc or a mixture thereof. The pair of enantiomers thus obtained may be separated 35 into individual stereoisomers by conventional means, for example by the use of an optically active amine as a resolving agent or on a chiral HPLC column.

Alternatively, any enantiomer of a compound of the general Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration.

5 Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, 10 sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethyl-15 aminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methyl-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, 25 maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Utilities

30 The compounds of the invention are antagonists of the EP4 receptor and are therefore useful in treating EP4 receptor mediated diseases.

In view of their ability to bind to the EP4 receptor, the compounds of the invention are useful in the treatment of the disorders that follow. Thus, the compounds of the invention are useful as analgesics. For example they are useful in the treatment of chronic 35 articular pain (e.g. rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis and

juvenile arthritis) including the property of disease modification and joint strucure 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 5 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 the invention are useful in the treatment of neuropathic pain. Neuropathic pain syndromes can develop following neuronal injury and the resulting pain may 10 persist for months or years, even after the original injury has healed. Neuronal injury may occur in the peripheral nerves, dorsal roots, spinal cord or certain regions in the brain. Neuropathic pain syndromes are traditionally classified according to the disease or event that 25 precipitated them. Neuropathic pain syndromes include: diabetic neuropathy; sciatica; non-specific lower back pain; multiple sclerosis pain; fibromyalgia; HIV related neuropathy; post-herpetic neuralgia; trigeminal 15 neuralgia; and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions. These conditions are difficult to treat and although several drugs are known to have limited efficacy, complete pain control is rarely achieved. The symptoms of neuropathic pain are incredibly heterogeneous and are often described as spontaneous shooting and lancinating pain, or ongoing, burning pain. In addition, there is pain associated with normally 20 non-painful sensations such as "pins and needles" (paraesthesia and dysesthesia), 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 25 stimulation (hyperpathia) or an absence of or deficit in selective sensory pathways (hypoalgesia).

The compounds of the invention are also useful in the treatment of inflammation, for example in the treatment of skin conditions (e.g. sunburn, burns, eczema, dermatitis, 30 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, CORD); 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); organ transplantation; other 35 conditions with an inflammatory component such as vascular disease, migraine, periarthritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, sclerodoma, myasthenia gravis, multiple sclerosis, sarcoidosis, nephrotic syndrome, Bechet's syndrome, polymyositis, gingivitis,

myocardial ischemia, pyrexia, systemic lupus erythematosus, polymyositis, tendinitis, bursitis, and Sjogren's syndrome.

The compounds of the invention are also useful in the treatment of immunological diseases such as autoimmune diseases, immunological deficiency diseases or organ transplantation. The compounds of the invention are also effective in increasing the latency of HIV infection.

The compounds of the invention are also useful in the treatment of diseases of abnormal platelet function (e.g. occlusive vascular diseases).

The compounds of the invention are also useful for the preparation of a drug with diuretic action.

The compounds of the invention are also useful in the treatment of impotence or erectile dysfunction.

The compounds of the invention are also useful in the treatment of bone disease characterized 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, cancer cachexia, calculosis, lithiasis (especially urolithiasis), solid carcinoma, gout and ankylosing spondylitis, tendinitis and bursitis. In a further aspect compounds of the invention may be useful in inhibiting bone resorption and/or promoting bone generation.

The compounds of the invention are also useful for attenuating the hemodynamic side effects of NSAIDs and COX-2 inhibitors.

The compounds of the invention are also 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 the invention are also useful in the treatment of neurodegenerative diseases and neurodegeneration 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, 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 are also useful in the treatment of neuroprotection and in the treatment of neurodegeneration following stroke, cardiac arrest, pulmonary bypass, traumatic brain injury, spinal cord injury or the like.

5 The compounds of the invention are also useful in the treatment of tinnitus.

The compounds of the invention are also useful in preventing or reducing dependence on, or preventing or reducing tolerance or reverse tolerance to, a dependence - inducing agent. Examples of dependence inducing agents include opioids (e.g. morphine), CNS depressants (e.g. ethanol), psychostimulants (e.g. cocaine) and nicotine.

10 The compounds of the invention are also 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.

15 The compounds of the invention are also useful in the treatment of kidney dysfunction (nephritis, particularly mesangial proliferative glomerulonephritis, nephritic syndrome), liver dysfunction (hepatitis, cirrhosis), gastrointestinal dysfunction (diarrhoea) and colon cancer.

20 The compounds of the invention are also useful for treating or preventing a neoplasia in a subject in need of such treatment or prevention. The term "treatment" includes partial or total inhibition of the neoplasia growth, spreading or metastasis, as well as partial or 25 total destruction of the neoplastic cells. The term "prevention" includes either preventing the onset of clinically evident neoplasia altogether or preventing the onset of a preclinically evident stage of neoplasia in individuals at risk. Also intended to be encompassed by this definition is the prevention of initiation for malignant cells or to arrest or reverse the progression of premalignant cells to malignant cells. This includes prophylactic treatment of those at risk of developing the neoplasia. The term "subject" for purposes of treatment includes any human or mammal subject 30 who has any one of the known neoplasias, and preferably is a human subject. For methods of prevention, the subject is any human or animal subject, and preferably is a human subject who is at risk for obtaining a neoplasia. The subject may be at risk due to exposure to carcinogenic agents, being genetically predisposed to have the neoplasia, and the like.

35 The term "neoplasia" includes both benign and cancerous tumors, growths and polyps. Thus, the compounds of the invention are useful for treating or preventing benign tumors, growths and polyps including squamous cell papilloma, basal cell tumor, transitional cell papilloma, adenoma, gastrinoma, cholangiocellular adenoma, hepatocellular adenoma, renal tubular adenoma, oncocytoma, glomus tumor, melanocytic nevus, fibroma, myxoma, lipoma, leiomyoma, rhabdomyoma, benign teratoma, hemangioma, osteoma, chondroma and

meningioma. The compounds of the invention are also useful for treating or preventing cancerous tumors, growths and polyps including squamous cell carcinoma, basal cell carcinoma, transitional cell carcinoma, adenocarcinoma, malignant gastrinoma, cholangiocellular carcinoma, hepatocellular carcinoma, renal cell carcinoma, malignant melanoma, fibrosarcoma, 5 myxosarcoma, liposarcoma, leimyosarcoma, rhabdomyosarcoma, malignant teratoma, hemangiosarcoma, Kaposi sarcoma, lymphangiosarcoma, osteosarcoma, chondrosarcoma, malignant meningioma, non-Hodgkin lymphoma, Hodgkin lymphoma and leukemia. For purposes of this specification, "neoplasia" includes brain cancer, bone cancer, epithelial cell-derived neoplasia (epithelial carcinoma), basal cell carcinoma, adenocarcinoma, gastrointestinal 10 cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, rectal cancer, liver cancer, bladder cancer, pancreas cancer, ovary cancer, cervical cancer, lung cancer, breast cancer and skin cancer, such as squamous cell and basal cell cancers, prostate cancer, renal cell carcinoma, and other known cancers that affect epithelial, mesenchymal or blood cells throughout the body. The compounds of the invention are useful for 15 treating or preventing any of the aforementioned cancers. The compounds of the invention are useful for treating or preventing benign and cancerous tumors, growths and polyps of the following cell types: squamous epithelium, basal cells, transitional epithelium, glandular epithelium, G cells, bile ducts epithelium, hepatocytes, tubules epithelium, melanocytes, fibrous connective tissue, cardiac skeleton, adipose tissue, smooth muscle, skeletal muscle, germ cells, 20 blood vessels, lymphatic vessels, bone, cartilage, meninges, lymphoid cells and hematopoietic cells. The compounds can be used to treat subjects having adenomatous polyps, including those with familial adenomatous polyposis (FAP). Additionally, the compounds can be used to prevent polyps from forming in patients at risk of FAP. Preferably, the compounds of the invention are useful for treating or preventing the following cancers: colorectal, esophagus stomach, breast, 25 head and neck, skin, lung, liver, gall bladder, pancreas, bladder, endometrium cervix, prostate, thyroid and brain.

It is to be understood that reference to treatment includes both treatment of established symptoms and prophylactic treatment, unless explicitly stated otherwise.

30 Dose Ranges

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature and severity of the condition to be treated, and with the particular compound of Formula I used and its route of administration. The dose will also vary according to the age, weight and response of the individual patient. In general, the daily dose 35 range lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a

mammal, preferably 0.01 mg to about 50 mg per kg, and most preferably 0.1 to 10 mg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

5 For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.01 mg to about 25 mg (preferably from 0.1 mg to about 10 mg) of a compound of Formula I per kg of body weight per day.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 100 mg of a compound of Formulas I or I a per kg of body weight per day, preferably from about 0.1 mg to about 10 mg per kg.

10 For use where a composition for sublingual administration is employed, a suitable dosage range is from 0.01 mg to about 25 mg (preferably from 0.1 mg to about 5 mg) of a compound of Formula I per kg of body weight per day.

Pharmaceutical Compositions

15 Another aspect of the present invention provides pharmaceutical compositions which comprises a compound of Formula I and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from 20 combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of Formula I, additional active ingredient(s), and pharmaceutically acceptable excipients.

25 Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, sublingual, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

30 The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, sublingual, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (aerosol inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and 5 on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulizers. The compounds may also be delivered as powders which may be formulated and the 10 powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery systems for inhalation are metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of a compound of Formula I in suitable propellants, such as fluorocarbons or hydrocarbons and dry powder inhalation (DPI) aerosol, which may be formulated as a dry powder of a compound of Formula I with or without additional excipients.

15 Suitable topical formulations of a compound of formula I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active 20 ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid 25 preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because 30 of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of 5 pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired 10 presentation. For example, a tablet may be prepared by compression or molding, 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 powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered 15 compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 1 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 1 to about 500 mg of the active ingredient.

Combination Therapy

Compounds of Formula I may be used in combination with other drugs that are 20 used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other 25 drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of Formula I. Examples of other active ingredients that may be combined with a compound of Formula I, either administered separately or in the same pharmaceutical compositions, include, 30 but are not limited to: COX-2 inhibitors, such as celecoxib, rofecoxib, etoricoxib, valdecoxib or parecoxib; 5- lipoxygenase inhibitors; NSAIDs, such as diclofenac, indomethacin, nabumetone or ibuprofen; leukotriene receptor antagonists; DMARDs such as methotrexate; adenosine A1 receptor agonists; sodium channel blockers, such as lamotrigine; NMDA receptor modulators, such as glycine receptor antagonists; gabapentin and related compounds; tricyclic antidepressants 35 such as amitriptyline; neurone stabilising antiepileptic drugs; mono-aminergic uptake inhibitors

such as venlafaxine; opioid analgesics; local anaesthetics; 5HT agonists, such as triptans, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, frovatriptan, almotriptan or rizatriptan; EP1 receptor ligands; EP2 receptor ligands; EP3 receptor ligands; EP1 antagonists; EP2 antagonists and EP3 antagonists. When the compounds are used in combination with other 5 therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of Formula I or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

10 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 15 formulations.

20 The weight ratio of the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of Formula I is combined with an NSAID the weight ratio of the compound of Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of Formula I and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

25 Assays For Determining Biological Activity

The compounds of Formula I can be tested using the following assays to determine their prostanoid antagonist or agonist activity *in vitro* and *in vivo* and their selectivity. The prostanoid receptor activities demonstrated are DP, EP1, EP2, EP3, EP4, FP, IP and TP.

30 Stable expression of prostanoid receptors in the human embryonic kidney (HEK) 293(ebna) cell line

Prostanoid receptor cDNAs corresponding to full length coding sequences are subcloned into the appropriate sites of mammalian expression vectors and transfected into HEK 293(ebna) cells. HEK 293(ebna) cells expressing the individual cDNAs are grown under

selection and individual colonies are isolated after 2-3 weeks of growth using the cloning ring method and subsequently expanded into clonal cell lines.

Prostanoid receptor binding assays

5 Transfected HEK 293(ebna) cells are maintained in culture, harvested and membranes are prepared by differential centrifugation, following lysis of the cells in the presence of protease inhibitors, for use in receptor binding assays. Prostanoid receptor binding assays (for DP1, DP2 (CRTH2), EP1, EP2, EP3-III, EP4, FP, IP, and TP) are performed in 10 mM MES/KOH (pH 6.0) (EPs, FP and TP) or 10 mM HEPES/KOH (pH 7.4) (DPs and IP),
10 containing 1 mM EDTA, 2.5-30 mM divalent cation and the appropriate radioligand. Synthetic compounds are added in dimethylsulfoxide which is kept constant at 1 % (v/v) in all incubations. The reaction is initiated by addition of membrane protein. Non-specific binding is determined in the presence of 10 μ M of the corresponding non-radioactive prostanoid. Incubations are conducted for 60-120 min at room temperature or 30 °C and terminated by rapid filtration.
15 Specific binding is calculated by subtracting non specific binding from total binding. The residual specific binding at each ligand concentration is calculated and expressed as a function of ligand concentration in order to construct sigmoidal concentration-response curves. The binding affinity of the compounds is determined by calculating the equilibrium inhibition constant (K_i) from the equation $K_i=InPt/1+[radioligand]/K_d$ where K_d is the equilibrium dissociation constant
20 for the radioligand:receptor interaction and $InPt$ is the inflection point of the dose-response curves.

Examples 1 to 19 were tested in the above binding assay for the EP4 receptor and demonstrated IC₅₀s of less than 500 nM.

25 Prostanoid receptor agonist and antagonist assays

Whole cell second messenger assays measuring stimulation of intracellular cAMP accumulation in HEK-293(ebna)-hEP4 cells are performed to determine whether receptor ligands are agonists or antagonists. Cells are harvested and resuspended in HBSS containing 25 mM HEPES, pH 7.4. Incubations contain 0.5 mM IBMX (phosphodiesterase inhibitor, available
30 from Biomol). Samples are incubated at 37°C for 10 min, the reaction is terminated and cAMP levels are then measured. Ligands are added in dimethylsulfoxide which is kept constant at 1 % (v/v; agonists) or 2% (v/v; antagonists) in all incubations. For agonists, second messenger responses are expressed as a function of ligand concentration and both EC₅₀ values and the maximum response as compared to a PGE₂ standard are calculated. For antagonists, the ability
35 of a ligand to inhibit an agonist response is determined by carrying out dose-response curves in

the presence of PGE₂ agonist at a concentration corresponding to its EC₇₀. IC₅₀ values are calculated as the concentration of ligand required to inhibit 50% of the PGE₂-induced activity.

In the EP4 receptor antagonist assay, the compounds of Examples 1 to 19 showed an EC₅₀ of less than 1000 nM.

5

Rat Paw Edema Assay

The method is the same as described in Chan *et al* (J. Pharmacol. Exp. Ther. 274: 1531-1537, 1995).

10 Acute Inflammatory Hyperalgesia Induced by Carrageenan in Rats

The method is the same as described in Boyce *et al* (Neuropharmacology 33: 1609-1611, 1994).

Adjuvant-Induced Arthritis in Rats

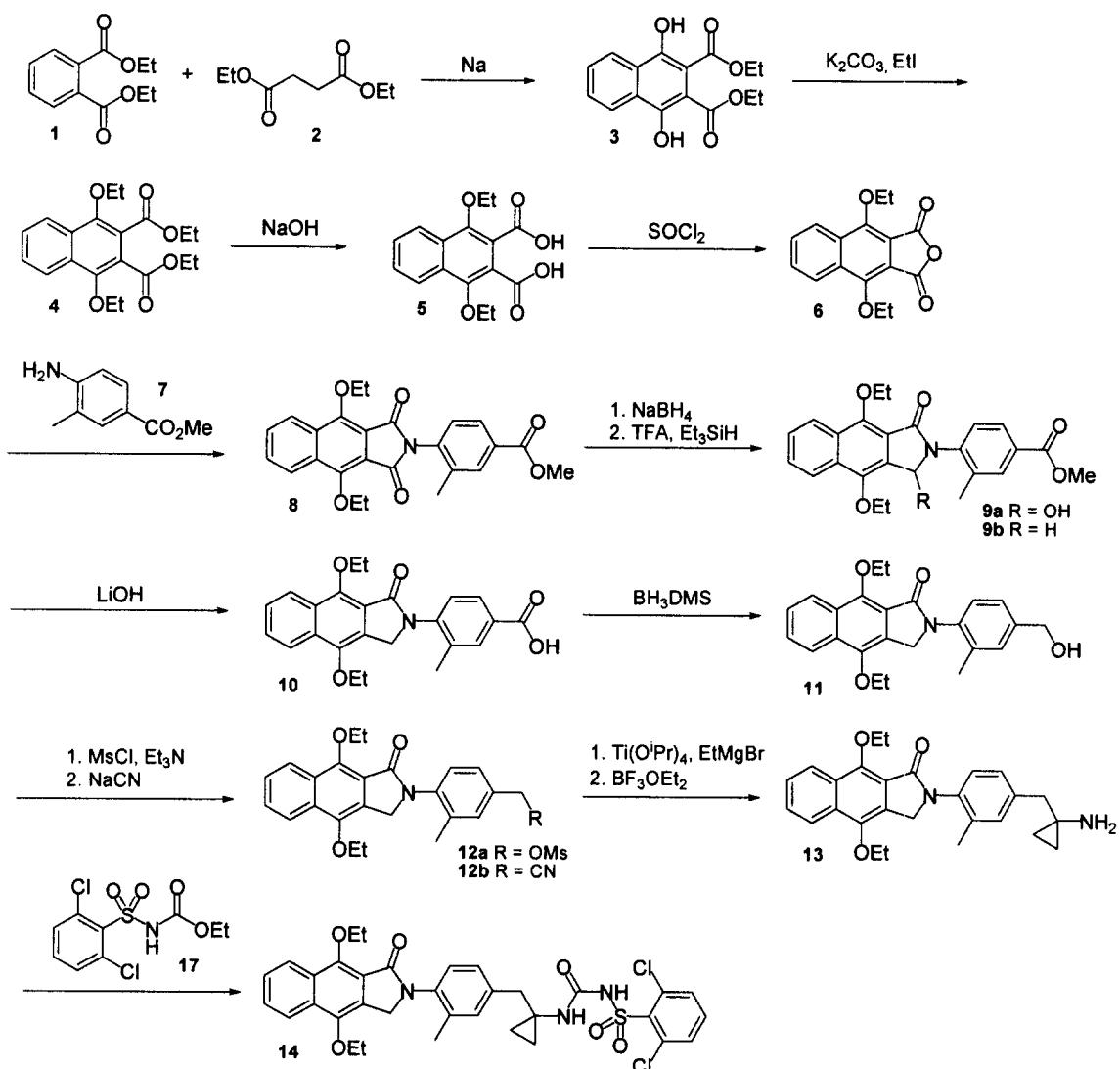
15 Female Lewis rats (body weight ~146-170 g) are weighed, ear marked, and assigned to groups (a negative control group in which arthritis was not induced, a vehicle control group, a positive control group administered indomethacin at a total daily dose of 1 mg/kg and four groups administered with a test compound at total daily doses of 0.001-10.0 mg/kg) such that the body weights were equivalent within each group. Six groups of 10 rats each are injected
20 into a hind paw with 0.5 mg of *Mycobacterium butyricum* in 0.1 mL of light mineral oil (adjuvant), and a negative control group of 10 rats was not injected with adjuvant. Body weights, contralateral paw volumes (determined by mercury displacement plethysmography) and lateral radiographs (obtained under Ketamine and Xylazine anesthesia) are determined before (day -1) and 17 to 21 days following adjuvant injection, and primary paw volumes are determined before
25 (day -1) and on days 4 and 17 to 21 following adjuvant injection. The rats are anesthetized with an intramuscular injection of 0.03 - 0.1 mL of a combination of Ketamine (87 mg/kg) and Xylazine (13 mg/kg) for radiographs and injection of adjuvant. The radiographs are made of both hind paws on day 0 and day 17-21 using the Faxitron (45 kVp, 30 seconds) and Kodak X-
30 OMAT TL film, and are developed in an automatic processor. Radiographs are evaluated for changes in the soft and hard tissues by an investigator who was blinded to experimental treatment. The following radiographic changes are graded numerically according to severity: increased soft issue volume (0-4), narrowing or widening of joint spaces (0-5) subchondral erosion (0-3), periosteal reaction (0-4), osteolysis (0-4) subluxation (0-3), and degenerative joint changes (0-3). Specific criteria are used to establish the numerical grade of severity for each
35 radiographic change. The maximum possible score per foot was 26. A test compound at total

daily doses of 0.1, 0.3, 1, and 3 mg/kg/day, indomethacin at a total daily dose of 1 mg/kg/day, or vehicle (0.5% methocel in sterile water) are administered per os b.i.d. beginning post injection of adjuvant and continuing for 17 to 21 days. The compounds are prepared weekly, refrigerated in the dark until used, and vortex mixed immediately prior to administration.

5

Method of Synthesis and Examples

Scheme 1.

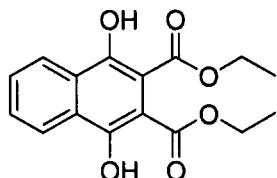


10

EXAMPLE 1

2,6-Dichloro-N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide

5

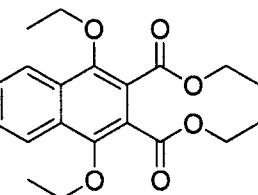


Diethyl 1,4-dihydroxynaphthalene-2,3-dicarboxylate (3) EtOH (200 mL) was added slowly to the solid sodium (24 g, 1044 mmol) and the mixture was stirred until most of the sodium had dissolved. The phthalate **1** (448 g, 2.02 mol) was then added, and the mixture was heated to 120 °C. The succinate **2** (88.0 g, 507 mmol) was then added over 1.5 hours via dropping funnel, then a stillhead was attached and heating continued for an additional 90 minutes while EtOH (150 mL) was collected. The resulting suspended solid mixture was dissolved in H₂O (700 mL) and benzene (700 mL). The layers were separated and the benzene layer was further extracted with 0.5 N NaOH(aq) (300 mL). The combined aqueous extracts were acidified and extracted with Et₂O (2 x 800 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting oily orange solid was dissolved in EtOH (400 mL), conc. HCl (aq) (10 mL) was added, followed by ice. The resulting mixture was heated and allowed to cool. The resulting solid was removed by filtration and was washed with cold water. The solid was dissolved in CH₂Cl₂ (500 mL) and washed with brine (500 mL). The organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 30 g of pure diphenol **3** (19.5% yield).

10

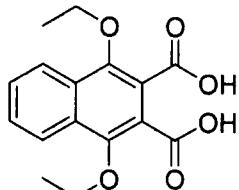
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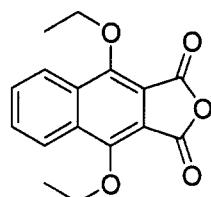
Diethyl 1,4-diethoxynaphthalene-2,3-dicarboxylate (4) To a solution of the diphenol **3** (30 g, 99 mmol) in DMF (197 mL) was added EtI (19.9 mL, 246 mmol) and K₂CO₃ (30 g, 217 mmol)

and the mixture was heated to reflux for 2 hours. The mixture was then cooled to rt and poured into H₂O (2.5 L). The aqueous layer was split in two, and each was extracted with Et₂O (2 x 750 mL). The combined ethereal extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting brown oil was dried in vacuo overnight to provide 13.5 g of pure diether as 5 a light brown solid. The two split aqueous layers from above were saturated with NaCl, and extracted again with Et₂O (2 x 750 mL). The combined ethereal extracts were dried over Na₂SO₄, filtered, concentrated in vacuo and azeotroped with heptane (3 x 200 mL) to provide an additional 5.8 g of pure diether **4** as a darker brown solid (54.3% yield).



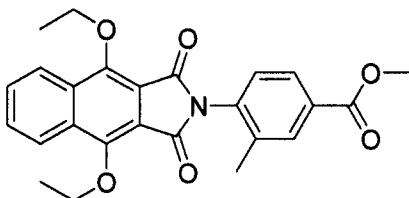
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Diethyl 1,4-dihydroxynaphthalene-2,3-dicarboxylate (5) To a solution of the diester **4** (19.3 g, 53.6 mmol) in EtOH (100 mL) was added the NaOH solution (16.1 mL, 10 M, 161 mmol) and water (33.5 mL). The mixture was heated to 60 °C with spinning on the rotovap for 90 minutes. After cooling to rt, EtOH was removed in vacuo, the mixture was acidified with 1 N HCl (300 mL) and extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to provide pure diacid **5** as a brown solid which was used directly without further purification.



20 **4,9-Diethoxynaphtho[2,3-c]furan-1,3-dione (6)** To a solution of the diacid **5** (16.3 g, 53.6 mmol) in CHCl₃ (134 mL) was added SOCl₂ (5.86 mL, 80.0 mmol) and this mixture was heated to reflux overnight. After cooling to rt, the mixture was concentrated in vacuo. Trituration of the resulting oily solid with ether/hexanes provided 10.0 g of pure anhydride as a light brown

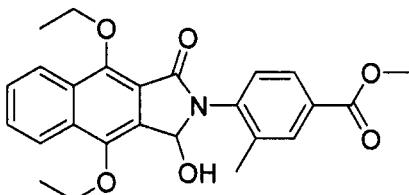
solid. Concentration of the filtrate and re-trituration provided an additional 1.3 g of anhydride **6** as a slightly darker brown solid (73.7% yield).



Methyl 4-(4,9-diethoxy-1,3-dioxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzoate (8)

5 A solution of the anhydride **6** (15.2 g, 53.1 mmol) and aniline **7** (13.2 g, 80.0 mmol, 1.5 equiv) in AcOH (500 mL) was heated to reflux for 1.5 hours. An additional 1.7 equiv of aniline were added over 3.5 hours and reflux continued overnight. The mixture was concentrated in vacuo and purified twice by flash column chromatography (80:20 to 60:40 hexanes:EtOAc, linear gradient) to afford 13.8 g of pure succinamide **8** (55.6% yield).

10



Methyl 4-(4,9-diethoxy-1-hydroxy-3-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-

methylbenzoate (9a) A solution of the succinamide **8** (12.8 g, 29.5 mmol) in 2:1 THF:MeOH

(450 mL) was cooled to 0 °C, and NaBH₄ (1.7 g, 45 mmol) was added. After 90 minutes, TLC

15 analysis showed ~95% conversion so an additional ~200 mg of NaBH₄ was added and stirring

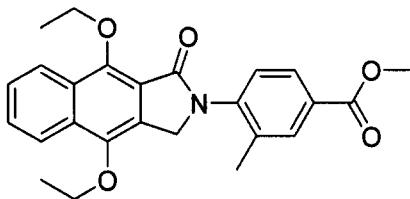
was continued for 20 minutes. The reaction was quenched by the addition of sat. NH₄Cl (200

mL) and the organic solvents were removed in vacuo. The resulting residue was diluted with

H₂O (200 mL) and extracted with CH₂Cl₂ (2 x 500 mL). The combined organic extracts were

dried over Na₂SO₄, filtered and concentrated in vacuo. The resulting aminal **9a**, a yellow foam,

20 was used directly without further purification.

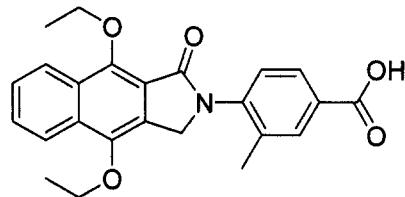


Methyl 4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzoate (9b)

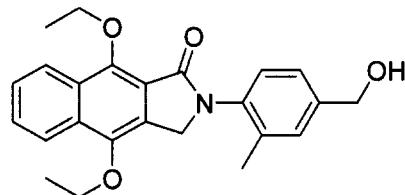
The aminal **9a** (12.9 g, 29.6 mmol) from the previous step was dissolved in TFA (296 mL)

resulting in the formation of a deep green solution. Et₃SiH (23.7 mL, 148 mmol) was then

5 added, and after stirring for 10 minutes at rt, the color had faded to orange. The mixture was concentrated in vacuo, then purified by flash column chromatography (load w/CH₂Cl₂; 80:20 to 60:40 hexanes:EtOAc, linear gradient) to provide 12.3 g of pure lactam **9b** (99% yield).



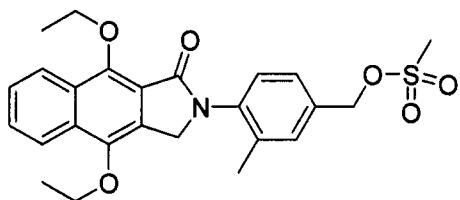
10 **4-(4,9-Diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzoic acid (10)** To a solution of the ester **9b** (12.3 g, 29.3 mmol) in THF/MeOH (176 mL : 58.6 mL) was added H₂O (58.6 mL) then the LiOH (2.46 g, 58.6 mmol). The mixture was stirred over 2.5 days at rt, at which point TLC analysis indicated complete conversion. The organic solvents were removed in vacuo and the aqueous layer was acidified with 1 N HCl (aq) (400 mL). The aqueous layer was 15 extracted with EtOAc (3 x 500 mL), the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to provide 12.0 g of pure acid **10** (100% yield).



4,9-Diethoxy-2-[4-(hydroxymethyl)-2-methylphenyl]-2,3-dihydro-1H-benzo[f]isoindol-1-one

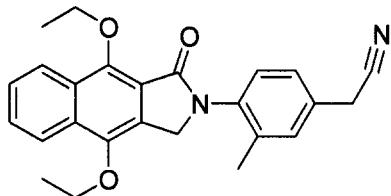
20 **(11)** To a solution of the acid **10** (11.8 g, 29.1 mmol) at rt was added BH₃·DMS (13.8 mL, 146

mmol) dropwise. The mixture was then stirred at RT for 4 hours, at which point TLC analysis indicated complete conversion. Excess BH_3 was quenched with MeOH and the mixture was concentrated in vacuo. The resulting residue was diluted and re-concentrated with MeOH (3 x 150 mL). Purification by flash column chromatography (load w/ CH_2Cl_2 ; 25:75 to 0:100 hexanes: EtOAc) provided 8.4 g of pure alcohol **11** as a white foam (73.7% yield).



4-(4,9-Diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl

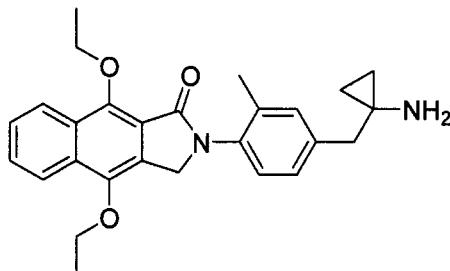
methanesulfonate (12a) A solution of the alcohol **11** (8.4 g, 22 mmol) in CH_2Cl_2 (86 mL) was cooled to 0 °C, then Et_3N (5.98 mL, 42.9 mmol) and MsCl (2.51 mL, 32.2 mmol) were added. After stirring at this temperature for 2 hours, TLC analysis indicated complete conversion to a mixture of two compounds. The mixture was diluted with EtOAc (700 mL) and washed with sat. NaHCO_3 (aq) (400 mL) and brine (400 mL). The aqueous fractions were further extracted with EtOAc (300 mL), then the combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo. Since insoluble material remained after this concentration, the mixture was re-diluted with CH_2Cl_2 (500 mL) and washed with sat. NaHCO_3 (aq) (500 mL). The aqueous layer was further extracted with CH_2Cl_2 (200 mL) and the combined organic extracts were dried over Na_2SO_4 , filtered and concentrated in vacuo. The mesylate **12a** was used in the subsequent step without further purification.



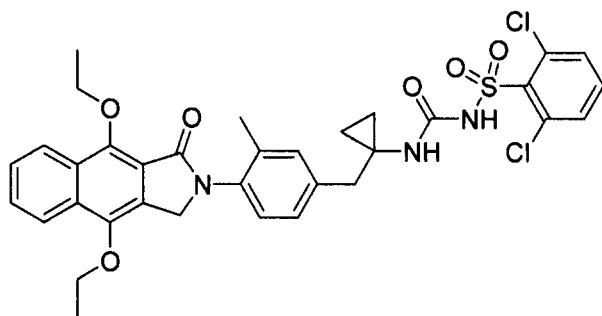
[4-(4,9-Diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylphenyl]acetonitrile

12b To a solution of the crude mesylate **12a** (10.1 g, 21.5 mmol) obtained in the previous step in DMF (100 mL) was added NaCN (5.26 g, 107 mmol). The mixture was stirred overnight,

resulting in the formation of an orange solution (with suspended solid). The mixture was diluted with Et₂O (400 mL) and washed with 1:1 H₂O: brine (3 x 400 mL). The aqueous fractions were further extracted with Et₂O (400 mL), then the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (load 5 w/CH₂Cl₂; 60:40 to 50:50 hexanes:EtOAc) provided 7.0 g of pure nitrile **12b** as a white solid (81% yield).



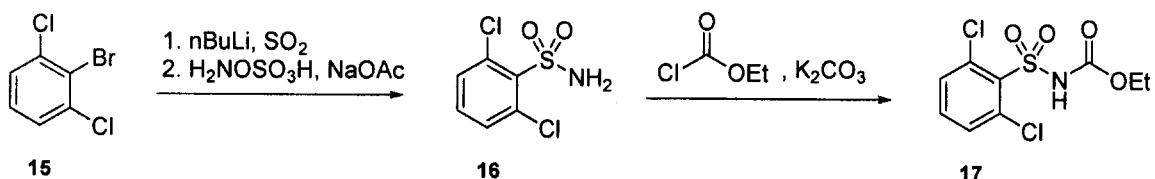
2-{4-[(1-Aminocyclopropyl)methyl]-2-methylphenyl}-4,9-diethoxy-2,3-dihydro-1H-benzo[f]isoindol-1-one (13) To a solution of the benzyl nitrile **12b** (500 mg, 1.25 mmol) in THF (16.6 mL) at rt was added titanium(IV) isopropoxide (0.92 mL, 3.1 mmol). The yellow solution was stirred for 5 min, followed by the addition of ethylmagnesium bromide (1.67 mL, 4.99 mmol, 3 M solution in ether). The brown solution was stirred at rt for 1 h and BF₃·OEt₂ (0.63 mL, 5.0 mmol) was added. The darker brown solution was stirred at rt for 30 min, quenched with 1 M NaOH (250 mL) and extracted with DCM (3x). Dry over Na₂SO₄, filter and concentrate. The 15 amine **13**, an orange foam, was used crude in the next reaction.



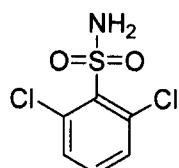
2,6-Dichloro-N-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino]carbonyl]benzenesulfonamide (14) A solution of crude cyclopropylamine **13** (538 mg, 1.25 mmol) and carbamate **17** (559 mg, 1.87 mmol) in DME (10 mL) was refluxed (90°C) overnight. The dark green solution was cooled to rt and quenched with 20

1 M HCl. Extract with EtOAc (3x), dry over Na_2SO_4 and concentrate the green solution. Purify by F-C (60% EtOAc/hexanes with AcOH, load with DCM) to afford a light orange foam. An ether swish afforded the desired compound **14** as a colorless solid (28.4% over 2 steps). ^1H NMR δ (ppm)(Acetone): 9.68 (1H, bs), 8.44 (1 H, d, J = 8.42 Hz), 8.26 (1 H, d, J = 8.41 Hz), 7.74-7.60 (5 H, m), 7.37 (1 H, d, J = 7.95 Hz), 7.17 (1 H, s), 7.05 (1 H, d, J = 8.07 Hz), 6.53 (1 H, s), 5.02 (2 H, s), 4.55 (2 H, q, J = 7.01 Hz), 4.33 (2 H, q, J = 7.00 Hz), 2.80 (2H, s), 2.28 (3 H, s), 1.51 (6 H, td, J = 7.00, 2.05 Hz), 0.88-0.82 (2 H, s), 0.77-0.71 (2 H, s). MS (+ESI): m/z 682.1 ($\text{M}+1$)⁺, 684.0.

10 **Scheme 2.** Preparation of ethyl sulfonylcarbamates.

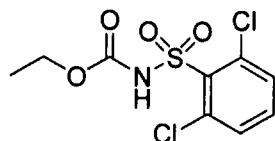


15



2,6-Dichlorobenzensulfonamide (**16**) To a solution of 1-bromo-2,6-dichlorobenzene **15** (21.2 g, 94.0 mmol) in THF (100 mL) at -78 °C was added n-BuLi (48.9 mL, 78.2 mmol, 1.6 M in hexanes). The reaction mixture was stirred at -78 °C for 2 hours. Sulfur dioxide was bubbled into the mixture for 15 min. The yellow solution was stirred overnight at 4°C, during which a colorless precipitate formed. The reaction was warmed to rt, hexanes was added and the sulfinic salt was filtered. The salt was dissolved in water (250 mL) and sodium acetate (16.0 g, 196 mmol) was added. The solution was cooled to 10 °C and hydroxylamine-*O*-sulfonic acid (11 g, 98 mmol) was added. The ice-water bath was removed and a white product precipitated out within minutes. The reaction was stirred for 3 hours. The reaction was extracted with EtOAc

(3x) and the combined organic layers were washed with 5% NaHCO₃. Dry over Na₂SO₄, filter and concentrate to afford the sulfonamide **16** a colorless solid. Use crude in next reaction.



5 **Ethyl [(2,6-dichlorophenyl)sulfonyl]carbamate (17)** To a heterogeneous solution of sulfonamide **16** (14.5 g, 64.1 mmol) and potassium carbonate (31.0 g, 224 mmol) in acetone (130 mL) was added ethyl chloroformate (15.4 mL, 160 mmol). The reaction was refluxed overnight. Quench with 1 M HCl and extract with EtOAc (3x). Dry over Na₂SO₄, filter and concentrate to afford 18.8 g of the carbamate **17** as a light yellow solid (98% yield).

10

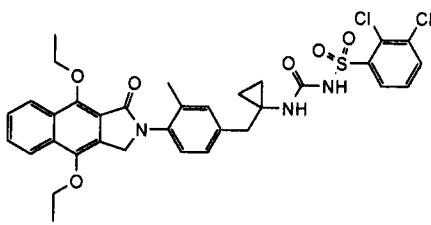
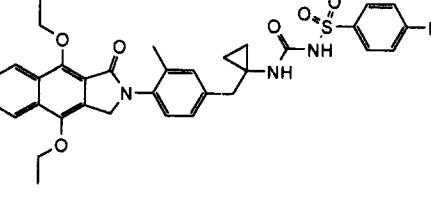
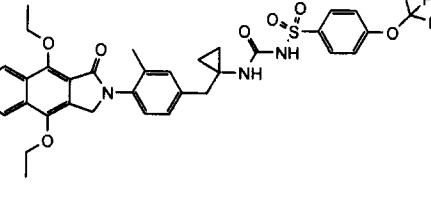
Following the method of Example 1, the compounds of Table 1 were prepared.

Table 1

Ex.	Name	Structure	MS (ESI)
2	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-4-methylbenzenesulfonamide		628.4 (M+1)
3	2-chloro- <i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-benzenesulfonamide		646.1 (M-1)

Ex.	Name	Structure	MS (ESI)
4	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-2-methylbenzenesulfonamide		628.1 (M+1)
5	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-2-methoxybenzenesulfonamide		644.1 (M+1)
6	2-bromo- <i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-benzenesulfonamide		692.1 694.1 (M+1)
7	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino)carbonyl]-2,6-dimethoxybenzenesulfonamide		674.2 (M+1)

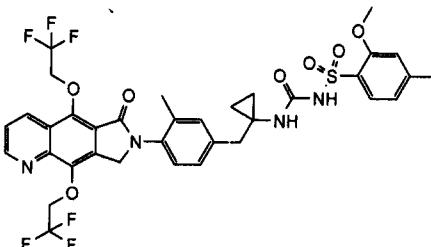
Ex.	Name	Structure	MS (ESI)
8	<i>N</i> -[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-(trifluoromethyl)benzenesulfonamide		682.1 (M+1)
9	<i>N</i> -[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-naphthalene-2-sulfonamide		664.1 (M+1)
10	<i>N</i> -[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-bis(trifluoromethyl)benzenesulfonamide		750.0 (M+1)
11	<i>N</i> -[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-dimethylbenzenesulfonamide		640.2 (M-1)

Ex.	Name	Structure	MS (ESI)
12	2,3-dichloro-N-[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino]carbonyl]benzenesulfonamide		682.0 683.9 (M+1)
13	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino]carbonyl]-4-fluorobenzenesulfonamide		632.1 (M+1)
14	<i>N</i> -[(1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2H-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl)amino]carbonyl]-4-(trifluoromethoxy)benzenesulfonamide		698.0 (M+1)

The compounds of Table 2 further exemplify the invention:

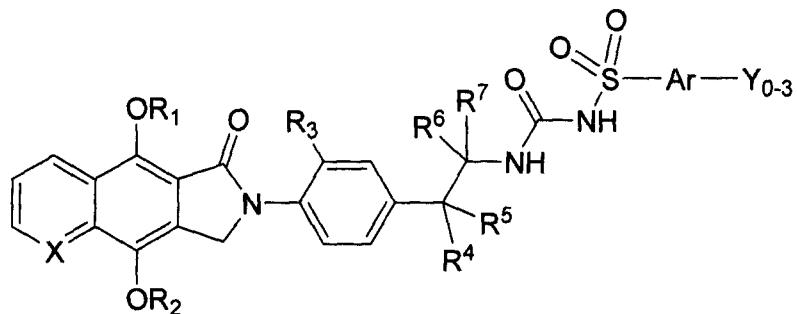
Table 2

Ex.	Name	Structure	MS (ESI)
15	<i>N</i> -{[(2-{4-[4,9-bis(difluoromethoxy)-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl]-3-methylphenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide		644.3 (M-1)
16	Hydrochloride salt of 2-chloro- <i>N</i> -{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7 <i>H</i> -pyrrolo[3,4-g]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}-4-methylbenzenesulfonamide		755.1 (M-1)
17	2-chloro- <i>N</i> -{[(2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2 <i>H</i> -benzo[<i>f</i>]isoindol-2-yl)-3-methylphenyl]-2,2-difluoroethyl)amino]carbonyl}-4-methylbenzenesulfonamide		658.0 (M+1)
18	<i>N</i> -{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7 <i>H</i> -pyrrolo[3,4-g]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}-naphthalene-2-sulfonamide		771.3 (M-1)

Ex.	Name	Structure	MS (ESI)
19	2-methoxy-4-methyl-N-[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7 <i>H</i> -pyrrolo[3,4- <i>g</i>]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl]benzenesulfonamide		766.9 (M+1)

WHAT IS CLAIMED IS:

1. A compound according of Formula I



5

I

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of N or CH;

10 R¹ and R² are independently selected from the group consisting of: C₁-6alkyl, C₃-6cycloalkyl, and C₁-6fluoroalkyl;

R³ is selected from the group consisting of: halogen, C₁-6alkyl and C₁-6haloalkyl;

15 R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of: hydrogen, halogen, C₁-6alkyl and C₃-6cycloalkyl; and R⁴ and R⁵ or R⁶ and R⁷ can join to make a 3-6 membered monocyclic cycloalkane ring;

20 Ar is selected from the group consisting of: C₃-6cycloalkyl, aryl, heteroaryl, and heterocyclyl, or a fused analog of C₃-6cycloalkyl, aryl, heteroaryl, and heterocyclyl; and

each Y is independently selected from the group consisting of: halo, methyl, ethyl, methoxy, CF₃, CF₃O- and hydroxy.

25 2. The compound according to Claim 1 wherein Ar is phenyl or naphthyl.

3. The compound according to Claim 2 wherein Ar is phenyl.

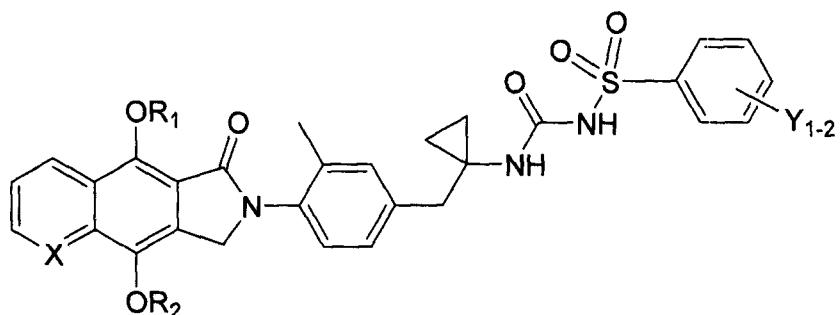
4. The compound according to Claim 1 wherein R³ is methyl.

5. The compound according to Claim 1 wherein: R⁴ and R⁵ are hydrogen and R⁶ and R⁷ are joined to make a cyclopropyl ring.

6. The compound according to Claim 1 wherein X is N.

7. The compound according to Claim 1 wherein X is CH.

10 8. The compound according to Claim 1 according to Formula Ia



Ia

15 or a pharmaceutically acceptable salt thereof, wherein:

X is selected from the group consisting of N or CH;

20 R¹ and R² are the same and selected from the group consisting of: ethyl, 2,2,2-trifluoroethyl and difluoromethyl; and

one or two Y groups are present and each Y is independently selected from the group consisting of: F, Cl, Br, methyl, ethyl, methoxy, CF₃, CF₃O- and hydroxy.

25 9. The compound according to Claim 8 wherein X is N.

10. The compound according to Claim 8 wherein X is CH.

11. The compound according to Claim 1 selected from the following group:

2,6-dichloro-*N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

5

N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-methylbenzenesulfonamide;

10 2-chloro-*N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl] benzenesulfonamide;

N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-methylbenzenesulfonamide;

15 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-methoxybenzenesulfonamide;

20 2-bromo-*N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

25 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-dimethoxybenzenesulfonamide;

N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2-(trifluoromethyl)benzenesulfonamide;

30 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]naphthalene-2-sulfonamide;

N-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-bis(trifluoromethyl)benzenesulfonamide;

5 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-2,6-dimethylbenzenesulfonamide;

10 2,3-dichloro-*N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]benzenesulfonamide;

15 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-fluorobenzenesulfonamide;

20 10 *N*-[({1-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylbenzyl]cyclopropyl}amino)carbonyl]-4-(trifluoromethoxy)benzenesulfonamide;

25 15 *N*-{[(2-{4-[4,9-bis(difluoromethoxy)-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl]-3-methylphenyl}ethyl)amino]carbonyl}-4-methylbenzenesulfonamide;

30 20 2-chloro-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide;

35 25 2-chloro-*N*-[({2-[4-(4,9-diethoxy-1-oxo-1,3-dihydro-2*H*-benzo[f]isoindol-2-yl)-3-methylphenyl]-2,2-difluoroethyl}amino)carbonyl] benzenesulfonamide;

40 30 *N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4-*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}naphthalene-2-sulfonamide; and

45 35 2-methoxy-4-methyl-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4-*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide;

50 40 or a pharmaceutically acceptable salt of any of the foregoing compounds.

12. The compound according to Claim 1 which is the hydrochloride salt of 2-chloro-*N*-{[(1-{3-methyl-4-[6-oxo-5,9-bis(2,2,2-trifluoroethoxy)-6,8-dihydro-7*H*-pyrrolo[3,4*g*]quinolin-7-yl]benzyl}cyclopropyl)amino]carbonyl}benzenesulfonamide.

5 13. A pharmaceutical composition comprising a compound according to Claim 1 in admixture with one or more physiologically acceptable carriers or excipients.

14. A compound according to Claim 1 or a pharmaceutically acceptable derivative thereof for use in human or veterinary medicine.

10 15. A method of treating a human or animal subject suffering from a condition which is mediated by the action of PGE2 at EP4 receptors, which method comprises administering to said subject an effective amount of a compound according to Claim 1.

15 16. The use of a compound according to Claim 1 for the manufacture of a therapeutic agent for the treatment of a condition which is mediated by the action of PGE2 at EP4 receptors.

20 17. A method for treating acute or chronic pain, migraine, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, gout, bursitis, ankylosing spondylitis, primary dysmenorrhea, cancer or atherosclerosis in a patient in need thereof comprising administering to the patient a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2008/000561

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **C07D 209/64** (2006.01), **A61K 31/4035** (2006.01), **A61K 31/4745** (2006.01), **C07D 471/04** (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: **C07D 209/64** (2006.01), **A61K 31/4035** (2006.01), **A61K 31/4745** (2006.01), **C07D 471/04** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
Canadian Patent Database, STN and Delphion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CA 2608214 (MERCK FROSST CANADA LTD.) 23 November, 2006. Whole document.	1 to 17
A	WO 02/50032 (GLAXO GROUP LIMITED) 27 June 2002. Whole document.	1 to 17

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :	
“A” document defining the general state of the art which is not considered to be of particular relevance	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“E” earlier application or patent but published on or after the international filing date	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“L” document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“O” document referring to an oral disclosure, use, exhibition or other means	“&” document member of the same patent family
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

17 June 2008 (17-06-2008)

Date of mailing of the international search report

4 July 2008 (04-07-2008)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer
Edith Éthier 819- 934-2325

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. Claim Nos. : 15 and 17

because they relate to subject matter not required to be searched by this Authority, namely :

Claims 15 and 17 are directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or uses of the compounds defined in claims 1 to 12.

2. Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. Claim Nos. :

because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2008/000561

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
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