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(71) Applicant (for all designated States except US): **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SPRINGER, John, Robert** [US/US]; Pfizer Global Research and Development, 200 Cambridge Park Drive, Cambridge, MA 01240 (US). **VAZQUEZ, Michael, Lawrence** [US/US]; Pfizer Global Research and Development, Eastern Point road, Groton, CT 06340 (US).

(74) Agents: **BENSON, Gregg, C.** et al.; Pfizer Inc., Eastern Point Road, MS 9114, Groton, CT 06340 (US).

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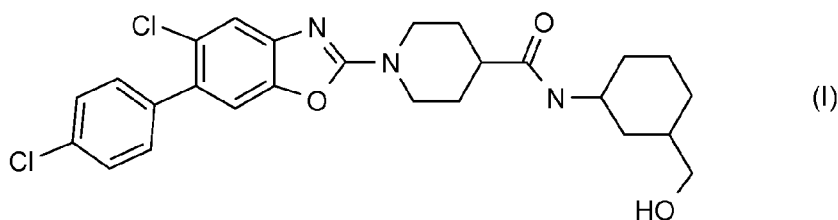
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(54) Title: PIPERIDINECARBOXAMIDES AS MPGES - 1 INHIBITORS



(57) Abstract: The invention relates to piperidinecarboxamides of formula (I), to their use in medicine as mPGES-1 inhibitors for the treatment of pain, to compositions containing them, to processes for their preparation and to intermediates used in such processes.

PIPERIDINECARBOXAMIDES AS MPGES-1 INHIBITORS

BACKGROUND OF THE INVENTION

5 The invention relates to piperidinecarboxamides, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes.

SUMMARY OF THE INVENTION

10 An unmet therapeutic need exists in the treatment of pain and inflammation which requires an improved analgesic activity relative to current COX-2 and NSAID inhibition therapies. Analgesic agents that display increased maximal inhibition of pain, safety, or utility in a broader population would provide benefit. Thus, development of a novel anti-inflammatory drug, with better safety and efficacy through an alternative
15 mechanism of action which would provide a different biochemical profile, is an urgent and challenging need.

 It has been well established that prostaglandin E2 (PGE2) is an important mediator in acute and chronic inflammation and pain (Kobayashi, T. et al. Prostaglandins and other lipid mediators 2002, 68, 552; Vanegas, H and Schaible, H.G.
20 Prostaglandins and cyclooxygenases in spinal cord; Prog.Neurobiology 2001, 64, 327; Ballou et al. PNAS USA 2000, 97, 10272). Prostaglandin synthase (PGHS) or more commonly cyclooxygenase (COX) is the enzyme that mediates biosynthesis of prostaglandins (PGs) and thromboxane (TxA2) from arachidonic acid, and whose inhibition underlies the effectiveness of a variety of anti-inflammatory drugs.

25 COX activity originates from two distinct and independently regulated isozymes, COX-1 and COX-2. COX-2 is inducible and is the major source of PGE2 which mediates pain and inflammation, while COX-1 catalyzes the formation of PGs that serve housekeeping functions, such as the maintenance of gastrointestinal (GI) integrity. Non-steroidal anti-inflammatory drugs (NSAIDs) are non-selective and inhibit both COX-
30 1 and COX-2, whereas coxibs are selective for COX-2. A few coxibs have been shown in controlled trials to reduce the incidence of serious gastrointestinal (GI) adverse effects when compared with traditional NSAIDs. Reduction of PGE2 production by the inhibition of COX-2 can remit the signs and symptoms of pain and edema associated with inflammation.

The enzyme microsomal prostaglandin E synthase type 1 (mPGES-1) occurs immediately downstream of COX-2 in the PGE2 pathway. It has recently been found to be up-regulated in response to inflammatory signals and is primarily responsible for the generation of PGE2 during inflammation. As PGE2 has been shown to be involved in arthritis and inflammation, mPGES-1 has been suggested as a new drug target.

The enzyme mPGES-1 is a member of the Membrane Associated Proteins in Eicosanoid and Glutathione metabolism (MAPEG) family of glutathione transferases, which also includes FLAP and LTC4 synthase. Murine knockouts of mPGES-1 demonstrate almost complete reduction of PGE2 from peritoneal macrophages stimulated with lipopolysaccharide (LPS) and complete reversal of the severity and incidence in collagen induced arthritis (Trebino, C. et al. PNAS USA 2003, 100(15), 9044). Therefore, a selective inhibitor of mPGES-1 would be expected to inhibit PGE2 production induced by inflammation, while sparing constitutive PGE2, prostacyclin (PGI2) and thromboxane (TxA2) production.

As noted above, a known consequence of non-selective COX inhibition has been adverse gastrointestinal effects; therefore, selective inhibitors of COX-2 were developed to inhibit the major enzymatic source of PGs which mediate pain and inflammation, while sparing PGs derived from COX-1 which contribute to gastric cytoprotection. Inhibitors of mPGES-1 would also inhibit the production of PGE2 from COX-2, but not PGI2 or PGs derived from COX-1 thereby avoiding GI effects.

However, by inhibiting COX -2 and the production of prostaglandin H2 (PGH2), all of the coxibs substantially depress the level of prostacyclin (PGI2), but leave platelet COX-1-derived thromboxane A2 (TxA2) levels unaffected. PGI2 is formed by prostacyclin synthase (PGIS) acting on the PGH2 formed by COX and is the major product of arachidonic acid in vascular endothelial cells. PGI2 inhibits platelet aggregation, vascular smooth muscle contraction and proliferation, leukocyte-endothelial cell interactions and cholesteryl ester hydrolase. It also activates reverse cholesterol transport. Deletion of the PGI2 receptor (IP) or suppression of PGI2 biosynthesis augments cardiac injury caused by ischemia/reperfusion. PGI2 also mediates the cardiovascular effects of thromboxane A2 (TxA2), the major COX-1 product of platelets. The cardiovascular effects of TxA2 include: platelet aggregation elevation of blood pressure and acceleration of atherogenesis.

Since mPGES-1 functions downstream of COX-2, selective inhibition of mPGES-1 does not interfere with the production of PGH2 and thus levels of PGI2, PGD2 and

TxA2 are also not inhibited. Accordingly, mPGES-1 inhibition has the potential to relieve pain and inflammation while minimizing any unwanted GI or CV adverse effects.

Certain mPGES-1 inhibitors are known. WO2009/098282 discloses certain thiophene derivatives said to be useful in the treatment of pain and inflammation.

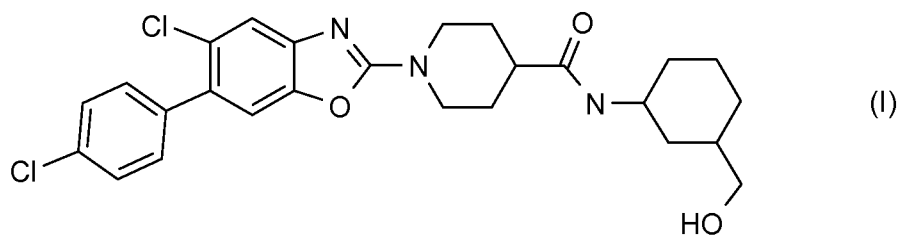
5 WO2008/084218 discloses certain benzazole derivatives also said to be useful in the treatment inflammation and inflammatory pain. WO2008/006663 discloses certain arylindole derivatives said to be useful in the treatment of a number of inflammatory processes and pain.

There is, however, an ongoing need to provide new mPGES-1 inhibitors that are
10 good drug candidates. In particular, such compounds should bind potently to mPGES-1 whilst showing little affinity for other enzymes and show functional activity as mPGES-1 inhibitors. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favourable pharmacokinetic properties (such as swift onset of action and minimal 'food effect'). They should be non-toxic and demonstrate
15 few side-effects. Furthermore, the ideal drug candidate will have good aqueous solubility and exist in a physical form that is stable, non-hygroscopic and easily formulated.

SUMMARY OF THE INVENTION

20 We have now found a new piperidinecarboxamide mPGES-1 inhibitor.

According to one aspect of the invention, therefore, there is provided the compound of formula (I)



25 or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Hereinafter, all references to compounds of the invention include the compound of formula (I) or pharmaceutically acceptable salt, solvate, or multi-component complex thereof, or pharmaceutically acceptable solvate or multi-component complex of a
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pharmaceutically acceptable salt of the compound of formula (I), as discussed in more detail below.

Suitable acid addition salts are formed from acids which form non-toxic salts.

Examples include the acetate, adipate, aspartate, benzoate, besylate,

5 bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, 10 pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminum, arginine, benzathine, calcium, choline, diethylamine, diolamine,

15 glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

The skilled person will appreciate that the aforementioned salts include ones 20 wherein the counterion is optically active, for example d-lactate or l-lysine, or racemic, for example dl-tartrate or dl-arginine.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

25 Pharmaceutically acceptable salts of the compound of formula (I) may be prepared by one or more of three methods:

- (i) by reacting the compound of formula (I) with the desired acid or base;
- (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula (I) using the desired acid or base; or
- 30 (iii) by converting one salt of the compound of formula (I) to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the

solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

The compound of formula (I) or pharmaceutically acceptable salts thereof may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of formula (I) or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. D₂O, d₆-acetone and d₆-DMSO.

A currently accepted classification system for organic hydrates is one that defines isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in Pharmaceutical Solids by K. R. Morris (Ed. H. G. Brittain, Marcel Dekker, 1995), incorporated herein by reference. Isolated site hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.

When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of the invention may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when

heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterised by a phase change, typically first order ('melting point').

Also included within the scope of the invention are multi-component complexes (other than salts and solvates) of the compound of formula (I) or pharmaceutically acceptable salts thereof wherein the drug and at least one other component are present in stoichiometric or non-stoichiometric amounts. Complexes of this type include clathrates (drug-host inclusion complexes) and co-crystals. The latter are typically defined as crystalline complexes of neutral molecular constituents which are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallisation, by recrystallisation from solvents, or by physically grinding the components together - see Chem Commun, 17, 1889-1896, by O. Almarsson and M. J. Zaworotko (2004), incorporated herein by reference. For a general review of multi-component complexes, see J Pharm Sci, 64 (8), 1269-1288, by Haleblan (August 1975), incorporated herein by reference.

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution). Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $\text{-COO}^-\text{Na}^+$, $\text{-COO}^-\text{K}^+$, or $\text{-SO}_3^-\text{Na}^+$) or non-ionic (such as $\text{-N}^+\text{N}^+(\text{CH}_3)_3$) polar head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970), incorporated herein by reference.

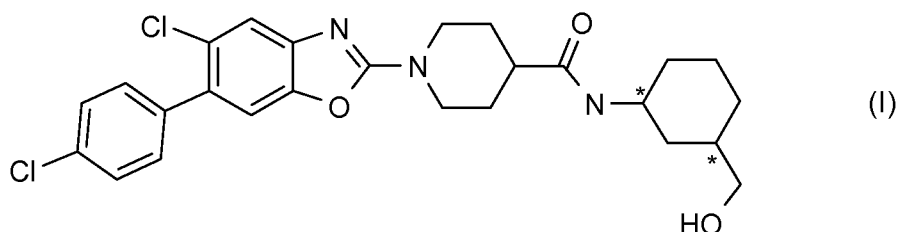
The compounds of the invention may be administered as prodrugs. Thus certain derivatives of the compound of formula (I) which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into the compound of formula (I) having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as 'prodrugs'. Further information on the use of prodrugs may be found in 'Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T Higuchi and W Stella) and 'Bioreversible Carriers in Drug Design', Pergamon Press, 1987 (ed. E B Roche, American Pharmaceutical Association).

Prodrugs can, for example, be produced by replacing appropriate functionalities present in the compound of formula (I) with certain moieties known to those skilled in the art as 'pro-moieties' as described, for example, in "Design of Prodrugs" by H Bundgaard (Elsevier, 1985).

5 Examples of prodrugs include phosphate prodrugs, such as dihydrogen or dialkyl (e.g. di-tert-butyl) phosphate prodrugs. Further examples of replacement groups in accordance with the foregoing examples and examples of other prodrug types may be found in the aforementioned references.

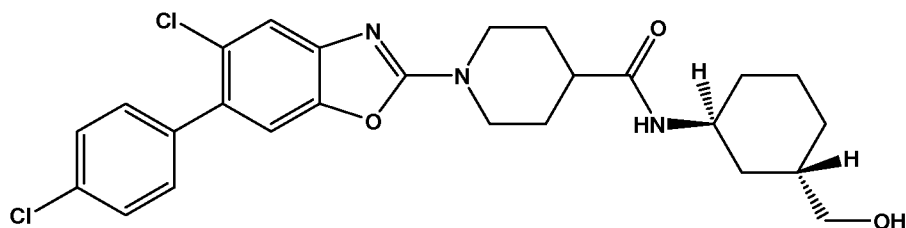
10 Also included within the scope of the invention are metabolites of compounds of formula (I), that is, compounds formed *in vivo* upon administration of the drug. Some examples of metabolites in accordance with the invention include, where the compound of formula (I) contains a phenyl (Ph) moiety, a phenol derivative thereof (-Ph > -PhOH);

15 Compounds of the invention containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. The skilled person will appreciate that the compound of formula (I) contains two such carbon atoms, as highlighted below where the asterisks (*) denotes the carbon atoms in question.



Included within the scope of the invention are all stereoisomers of the compounds of the invention and mixtures of one or more thereof.

20 Specifically, a compound of the invention is



25 Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC).

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula (I) contains an acidic or basic moiety, a base or acid such as 1-phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be
5 separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on
10 an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Mixtures of stereoisomers may be separated by conventional techniques known
15 to those skilled in the art; see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The scope of the invention includes all crystal forms of the compounds of the invention, including racemates and racemic mixtures (conglomerates) thereof. Stereoisomeric conglomerates may also be separated by the conventional techniques
20 described herein just above.

The scope of the invention includes all pharmaceutically acceptable isotopically-labelled compounds of the invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.

25 Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^2H and ^3H , carbon, such as ^{11}C , ^{13}C and ^{14}C , chlorine, such as ^{36}Cl , fluorine, such as ^{18}F , iodine, such as ^{123}I and ^{125}I , nitrogen, such as ^{13}N and ^{15}N , oxygen, such as ^{15}O , ^{17}O and ^{18}O , phosphorus, such as ^{32}P , and sulphur, such as ^{35}S .

30 Certain isotopically-labelled compounds of the invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^3H , and carbon-14, i.e. ^{14}C , are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e. ^2H , may

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. Substitution with positron emitting isotopes, such as ^{11}C , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compound of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Also within the scope of the invention are intermediate compounds as hereinafter defined, all salts, solvates and complexes thereof and all solvates and complexes of salts thereof as defined hereinbefore for the compound of formula (I). The invention includes all polymorphs of the aforementioned species and crystal habits thereof.

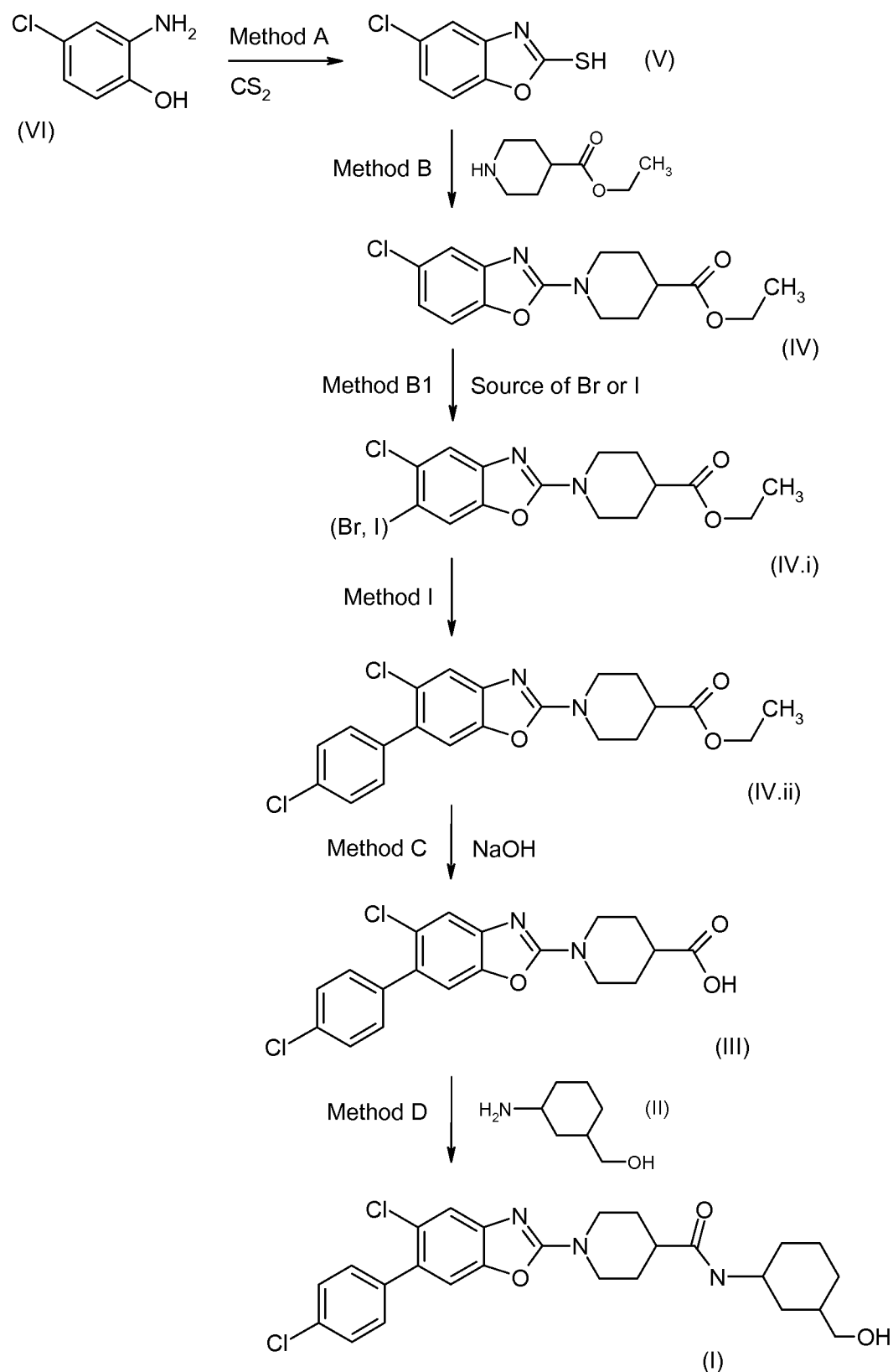
When preparing the compound of formula (I) in accordance with the invention, it is open to a person skilled in the art to routinely select the form of intermediate which provides the best combination of features for this purpose. Such features include the melting point, solubility, processability and yield of the intermediate form and the resulting ease with which the product may be purified on isolation.

The compounds of the invention may be prepared by any method known in the art for the preparation of compounds of analogous structure. In particular, the compounds of the invention can be prepared by the procedures described by reference to the Schemes that follow, or by the specific methods described in the Examples, or by similar processes to either.

The skilled person will appreciate that the experimental conditions set forth in the schemes that follow are illustrative of suitable conditions for effecting the transformations shown, and that it may be necessary or desirable to vary the precise conditions employed for the preparation of the compound of formula (I). It will be further appreciated that it may be necessary or desirable to carry out the transformations in a different order from that described in the schemes, or to modify one or more of the transformations, to provide the desired compound of the invention.

In addition, the skilled person will appreciate that it may be necessary or desirable at any stage in the synthesis of compounds of the invention to protect one or more sensitive groups, so as to prevent undesirable side reactions. In particular, it may be necessary or desirable to protect amino groups. The protecting groups used in the

preparation of the compounds of the invention may be used in conventional manner.
See, for example, those described in 'Greene's Protective Groups in Organic Synthesis'
by Theodora W Greene and Peter G M Wuts, fourth edition, (John Wiley and Sons,
2006), in particular chapter 7 ("Protection for the Amino Group"), incorporated herein by
5 reference, which also describes methods for the removal of such groups.

Scheme 1

Method A. Preparation of the benzoxazole-2-thiol of formula (V)

The aminophenol of formula (VI) (1.0 equivalent), carbon disulfide (2.0 equivalents) and potassium hydroxide (2.1 equivalents) are refluxed in ethanol overnight. The mixture is allowed to cool and concentrated *in-vacuo*. The residue is diluted with water and made acidic with 10% HCl. The resulting precipitate is filtered to give the benzoxazole-2-thiol of formula (V).

Alternate Method A. Preparation of the benzoxazole-2-thiol of formula (V)

The aminophenol of formula (VI) (1.0 equivalent), potassium O-ethylcarbonodithioate (1.0 equivalent) and pyridine (1.2 mL/mmol) are heated to reflux with condenser vented to bleach trap for 30 minutes. The reaction is cooled to room temperature and poured into concentrated HCl (0.5 mL/mmol) and ice water (2.5 mL/mmol). The mixture is stirred for 5 minutes, then filtered and the solid washed with H₂O. The solid is dissolved in EtOAc and washed with HCl, brine, and dried over Na₂SO₄. The EtOAc is filtered and concentrated to collect the solid benzoxazole-2-thiol of formula (V).

Method B. Preparation of the ethyl carboxylate of formula (IV)

The benzoxazole-2-thiol of formula (V) (1.0 equivalent) and ethyl isonipecotate (1.1 equivalents) in toluene are refluxed overnight. The mixture is allowed to cool and partitioned between EtOAc and water. The EtOAc layer is dried over Na₂SO₄ and concentrated in vacuo. The crude product is purified by silica gel flash chromatography (ethyl acetate/heptane) or reverse-phase HPLC (acetonitrile/water/0.1% trifluoroacetic acid) to give the ethyl carboxylate of formula (IV).

Method B1. Preparation of the bromo benzoxazole of formula (IV.i)

The ethyl carboxylate of formula (IV) (1.0 equivalent) is dissolved in acetic acid followed by the addition of bromine (1.0 equivalent). The solution is allowed to stir for 1 hour at room temperature. The reaction mixture is concentrated under vacuum and the residue filtered through a pad of silica gel, eluting with EtOAc/hexanes (10 – 25%) to give the bromo benzoxazole of formula (IV.i).

Alternate Method B.1. Preparation of the iodo benzoxazole of formula (IV.i)

The ethyl carboxylate of formula (IV) (25 g, 1.0 equivalent) is dissolved in acetic acid, N-iodosuccinimide (NIS) (1.1 equivalents) is added and the mixture is heated to ~45°C overnight. The reaction mixture is poured into water (700 mL) and extracted with CHCl₃ (2 x 600 mL, 1 x 300 mL). The organic extract is washed with 10% aq. NaHSO₃ (2 x 250 mL), saturated aq. K₂CO₃ (250 mL) and dried over Na₂SO₄ and concentrated under vacuum to give the iodo benzoxazole of formula (IV.i).

Method I. Preparation of the aryl substituted benzoxazole of formula (IV.ii)

The bromo (or iodo) benzoxazole of formula (IV.i) (1.0 equivalent), a boronic acid (1.1 to 5.0 equivalents), a Pd catalyst, such as tetrakis(triphenylphosphine)palladium (5 to 20%) and 2M aqueous sodium carbonate (2.0 equivalents) are refluxed in a suitable solvent, such as toluene/ethanol (2:1), DME/ethanol (2:1), or DMF, for 3 h to overnight. The mixture is allowed to cool and then partitioned between EtOAc and water. The organic layer is dried over Na₂SO₄ and concentrated in vacuo. The crude product is purified by flash silica gel (EtOAc/heptanes) to give the desired aryl substituted benzoxazole of formula (IV.ii).

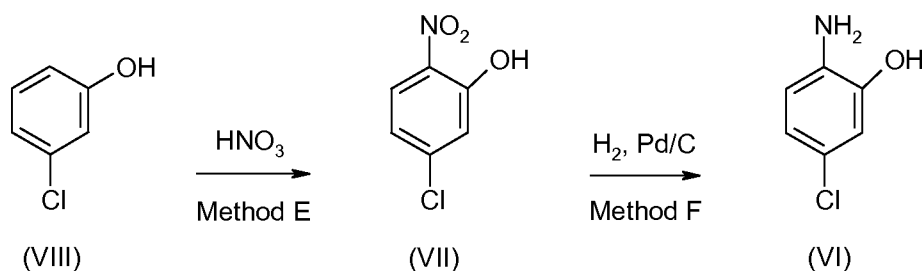
Method C. Preparation of the carboxylic acid of formula (III)

The ethyl carboxylate of formula (IV) (1.0 equivalent), 2.5 N sodium hydroxide (2.0 equivalents), methanol and water are stirred overnight. Methanol is removed under vacuum and the remaining solution is acidified with 10% aqueous HCl. The resulting solid is filtered to give the carboxylic acid of formula (III).

Method D. Preparation of the piperidinecarboxamide of formula (I)

2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (1.1 equivalents), followed by triethyl amine (1.1 equivalents), are added under nitrogen at room temperature to a solution of carboxylic acid of formula (III) (1.0 equivalent) in anhydrous dimethylformamide. The mixture is stirred for about five minutes and amine of formula (II) (1.5 equivalents) is added. The mixture is stirred for another hour, then filtered and purified by reverse-phase HPLC (acetonitrile/water/0.1% trifluoroacetic acid) to give the piperidinecarboxamides of formula (I).

Scheme 2 below shows the preparation of the aminophenol of formula (VI).

Scheme 2Method E. Preparation of 2-nitrophenol of formula (VII)

To the phenol of formula (VIII) (1 equivalent) in glacial acetic acid (1 mL/mmol) is added dropwise conc nitric acid (1.2 equivalents) in glacial acetic acid (1 mL/mmol). The contents are stirred for one hour and poured onto ice water. After stirring one hour, the solid is filtered to give the 2-nitrophenol of formula (VII).

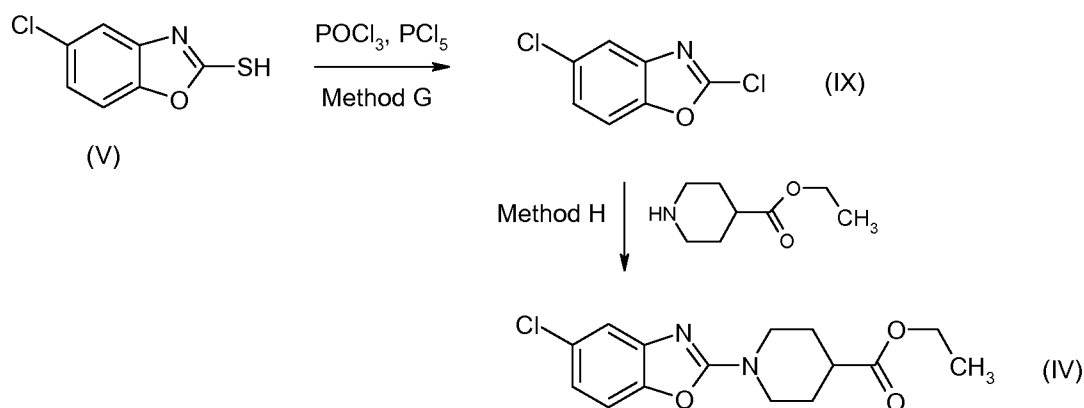
5 Method F. Preparation of 2-aminophenol of formula (VI)

The 2-nitrophenol of formula (VII) (1.0 equivalents), platinum (sulfided, 5% wt on carbon, reduced, dry, 4-5% weight) and methanol are stirred at 55 psi hydrogen overnight. The mixture is filtered through diatomaceous earth and the filtrate is concentrated *in-vacuo* to give the 2-aminophenol of formula (VI).

10

Scheme 3 below shows an alternative route for preparation of the compound of formula (IV).

Scheme 3



15

Method G. Preparation of 2-chloro-benzoxazole of formula (IX)

Phosphorous oxychloride (2.0 equivalents) and phosphorous pentachloride (1.0 equivalent) are added to the benzoxazole-2-thiol of formula (V) (1.0 equivalent) in acetonitrile. The mixture is refluxed six hours and concentrated *in vacuo*. The crude product is purified by flash silica gel (10%EtOAc/ heptanes) to give the 2-chloro-benzoxazole of formula (IX).

20

Alternate Method G

The benzoxazole-2-thiol of formula (V) (1 equivalent) is dissolved in CHCl_3 (1.5 mL/mmol) and stirred in an ice bath for 10 minutes. Chlorine gas is bubbled into the solution for 10 minutes. The reaction mixture is further stirred at room temperature overnight. The reaction mixture is poured into ice water (equal volume) and extracted

25

twice with aq. 2N NaOH, then ice water. The CHCl_3 solution is allowed to stand for 10 minutes, then filtered through a plug of silica gel to give clear solution. The solvent is removed under reduced pressure to afford the crude product. The crude product is dissolved CHCl_3 (25 mL) and filtered through diatomaceous earth. The solvent is removed under reduced pressure to give the solid 2-chloro-benzoxazole of formula (IX).

Method H. Preparation of the ethyl carboxylate of formula (IV)

To the 2-chloro-benzoxazole of formula (IX) (1 equivalent) in dichloromethane (1.3 mL/mmol) is added triethylamine (2.1 equivalents) and ethyl isonipecotate (1.05 equivalents) with stirring at room temperature overnight. The organic layer is washed with aq. 1N NaHCO_3 . The aqueous layer is extracted with CH_2Cl_2 . The organic layers are combined and dried over Na_2SO_4 and removed under reduced pressure to give the solid carboxylate of formula (IV).

In another aspect of the invention there is provided a process for preparing the compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises treating a carboxylic acid of formula (III) with an amine of formula (II).

In another aspect the invention provides a carboxylic acid of formulae (III).

Compounds of formulae (II) and (VIII) are either commercially available, known from the literature or easily prepared by methods well known to those skilled in the art.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products or may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term 'excipient' is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

In another aspect the invention provides a pharmaceutical composition comprising a compound of the invention together with one or more pharmaceutically acceptable excipients.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in "Remington's Pharmaceutical Sciences", 19th Edition (Mack Publishing Company, 1995).

Suitable modes of administration include oral, parenteral, topical, inhaled/intranasal, rectal/intravaginal, and ocular/aural administration.

Formulations suitable for the aforementioned modes of administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth. Formulations suitable for oral administration include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films, ovules, sprays, liquid formulations and buccal/mucoadhesive patches..

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, 11 (6), 981-986, by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium

carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinised starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, preferably from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinised starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from 0.25 weight % to 10 weight %, preferably from 0.5 weight % to 3 weight % of the tablet. Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant. Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated. The formulation of tablets is discussed in "Pharmaceutical Dosage Forms: Tablets", Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies

such as high energy dispersions and osmotic and coated particles are to be found in "Pharmaceutical Technology On-line", 25(2), 1-14, by Verma et al (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of the compound of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents. Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and poly(DL-lactic-co-glycolic) acid (PLGA) microspheres.

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, J Pharm Sci, 88 (10), 955-958, by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g. Powderject™, Bioject™, etc.) injection.

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurised container, pump, spray, atomiser (preferably an atomiser using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurised container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenisation, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomiser using electrohydrodynamics to produce a fine mist may contain from 1 µg to 20mg of the compound of the invention per actuation and the actuation volume may vary from 1 µl to 100 µl. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and

sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 1 µg to 100mg of the compound of formula (I). The overall daily dose will typically be in the range 1 µg to 200mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, microbicide, vaginal ring or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

The compounds of the invention may also be administered directly to the eye or ear, typically in the form of drops of a micronised suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments, biodegradable (e.g. absorbable gel sponges, collagen) and non-biodegradable (e.g. silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethylcellulose, hydroxyethylcellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the

cyclodextrin may be used as an auxiliary additive, i.e. as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

5 For administration to human patients, the total daily dose of the compounds of the invention is typically in the range 1mg to 10g, such as 10mg to 1g, for example 25mg to 500mg depending, of course, on the mode of administration and efficacy. For example, oral administration may require a total daily dose of from 50mg to 100mg. The total daily dose may be administered in single or divided doses and may, at the
10 physician's discretion, fall outside of the typical range given herein. These dosages are based on an average human subject having a weight of about 60kg to 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

 As noted above, the compounds of the invention are useful because they exhibit
15 pharmacological activity in animals, i.e., mPGES-1 inhibition. More particularly, the compounds of the invention are of use in the treatment of disorders for which a mPGES-1 inhibitor is indicated. Preferably the animal is a mammal, more preferably a human.

 In a further aspect of the invention there is provided a compound of the invention
20 for use as a medicament.

 In a further aspect of the invention there is provided a compound of the invention for the treatment of a disorder for which a mPGES-1 inhibitor is indicated.

 In a further aspect of the invention there is provided use of a compound of the invention for the preparation of a medicament for the treatment of a disorder for which a
25 mPGES-1 inhibitor is indicated.

 In a further aspect of the invention there is provided a method of treating a disorder in an animal (preferably a mammal) for which a mPGES-1 inhibitor is indicated, comprising administering to said animal a therapeutically effective amount of a compound of the invention.

30 Disorders for which a mPGES-1 inhibitor is indicated include pain, in particular inflammatory pain, such as pain associated with arthritis and neoplasias, in particular neoplasias that produce PGs or express a COX, including both benign and cancerous tumours, growths and polyps.

Physiological pain is an important protective mechanism designed to warn of danger from potentially injurious stimuli from the external environment. The system operates through a specific set of primary sensory neurones and is activated by noxious stimuli *via* peripheral transducing mechanisms (see Millan, 1999, Prog. Neurobiol., 57, 1-164 for a review). These sensory fibres are known as nociceptors and are characteristically small diameter axons with slow conduction velocities. Nociceptors encode the intensity, duration and quality of noxious stimulus and by virtue of their topographically organised projection to the spinal cord, the location of the stimulus. The nociceptors are found on nociceptive nerve fibres of which there are two main types, A-delta fibres (myelinated) and C fibres (non-myelinated). The activity generated by nociceptor input is transferred, after complex processing in the dorsal horn, either directly, or via brain stem relay nuclei, to the ventrobasal thalamus and then on to the cortex, where the sensation of pain is generated.

Pain may generally be classified as acute or chronic. Acute pain begins suddenly and is short-lived (usually twelve weeks or less). It is usually associated with a specific cause such as a specific injury and is often sharp and severe. It is the kind of pain that can occur after specific injuries resulting from surgery, dental work, a strain or a sprain. Acute pain does not generally result in any persistent psychological response. In contrast, chronic pain is long-term pain, typically persisting for more than three months and leading to significant psychological and emotional problems. Common examples of chronic pain are neuropathic pain (e.g. painful diabetic neuropathy, postherpetic neuralgia), carpal tunnel syndrome, back pain, headache, cancer pain, arthritic pain and chronic post-surgical pain.

When a substantial injury occurs to body tissue, *via* disease or trauma, the characteristics of nociceptor activation are altered and there is sensitisation in the periphery, locally around the injury and centrally where the nociceptors terminate. These effects lead to a heightened sensation of pain. In acute pain these mechanisms can be useful, in promoting protective behaviours which may better enable repair processes to take place. The normal expectation would be that sensitivity returns to normal once the injury has healed. However, in many chronic pain states, the hypersensitivity far outlasts the healing process and is often due to nervous system injury. This injury often leads to abnormalities in sensory nerve fibres associated with maladaptation and aberrant activity (Woolf & Salter, 2000, Science, 288, 1765-1768).

Clinical pain is present when discomfort and abnormal sensitivity feature among the patient's symptoms. Patients tend to be quite heterogeneous and may present with various pain symptoms. Such symptoms include: 1) spontaneous pain which may be dull, burning, or stabbing; 2) exaggerated pain responses to noxious stimuli (hyperalgesia); and 3) pain produced by normally innocuous stimuli (allodynia - Meyer et al., 1994, Textbook of Pain, 13-44). Although patients suffering from various forms of acute and chronic pain may have similar symptoms, the underlying mechanisms may be different and may, therefore, require different treatment strategies. Pain can also therefore be divided into a number of different subtypes according to differing pathophysiology, including nociceptive, inflammatory and neuropathic pain.

Nociceptive pain is induced by tissue injury or by intense stimuli with the potential to cause injury. Pain afferents are activated by transduction of stimuli by nociceptors at the site of injury and activate neurons in the spinal cord at the level of their termination. This is then relayed up the spinal tracts to the brain where pain is perceived (Meyer et al., 1994, Textbook of Pain, 13-44). The activation of nociceptors activates two types of afferent nerve fibres. Myelinated A-delta fibres transmit rapidly and are responsible for sharp and stabbing pain sensations, whilst unmyelinated C fibres transmit at a slower rate and convey a dull or aching pain. Moderate to severe acute nociceptive pain is a prominent feature of pain from central nervous system trauma, strains/sprains, burns, myocardial infarction and acute pancreatitis, post-operative pain (pain following any type of surgical procedure), posttraumatic pain, renal colic, cancer pain and back pain. Cancer pain may be chronic pain such as tumour related pain (e.g. bone pain, headache, facial pain or visceral pain) or pain associated with cancer therapy (e.g. postchemotherapy syndrome, chronic postsurgical pain syndrome or post radiation syndrome). Cancer pain may also occur in response to chemotherapy, immunotherapy, hormonal therapy or radiotherapy. Back pain may be due to herniated or ruptured intervertebral discs or abnormalities of the lumbar facet joints, sacroiliac joints, paraspinal muscles or the posterior longitudinal ligament. Back pain may resolve naturally but in some patients, where it lasts over 12 weeks, it becomes a chronic condition which can be particularly debilitating.

Neuropathic pain is currently defined as pain initiated or caused by a primary lesion or dysfunction in the nervous system. Nerve damage can be caused by trauma and disease and thus the term 'neuropathic pain' encompasses many disorders with diverse aetiologies. These include, but are not limited to, peripheral neuropathy,

diabetic neuropathy, post herpetic neuralgia, trigeminal neuralgia, back pain, cancer neuropathy, HIV neuropathy, phantom limb pain, carpal tunnel syndrome, central post-stroke pain and pain associated with chronic alcoholism, hypothyroidism, uremia, multiple sclerosis, spinal cord injury, Parkinson's disease, epilepsy and vitamin
5 deficiency. Neuropathic pain is pathological as it has no protective role. It is often present well after the original cause has dissipated, commonly lasting for years, significantly decreasing a patient's quality of life (Woolf and Mannion, 1999, Lancet, 353, 1959-1964). The symptoms of neuropathic pain are difficult to treat, as they are often heterogeneous even between patients with the same disease (Woolf & Decosterd,
10 1999, Pain Supp., 6, S141-S147; Woolf and Mannion, 1999, Lancet, 353, 1959-1964). They include spontaneous pain, which can be continuous, and paroxysmal or abnormal evoked pain, such as hyperalgesia (increased sensitivity to a noxious stimulus) and allodynia (sensitivity to a normally innocuous stimulus).

The inflammatory process is a complex series of biochemical and cellular events,
15 activated in response to tissue injury or the presence of foreign substances, which results in swelling and pain (Levine and Taiwo, 1994, Textbook of Pain, 45-56). Arthritic pain is the most common inflammatory pain. Rheumatoid disease is one of the commonest chronic inflammatory conditions in developed countries and rheumatoid arthritis is a common cause of disability. The exact aetiology of rheumatoid arthritis is
20 unknown, but current hypotheses suggest that both genetic and microbiological factors may be important (Grennan & Jayson, 1994, Textbook of Pain, 397-407). It has been estimated that almost 16 million Americans have symptomatic osteoarthritis (OA) or degenerative joint disease, most of whom are over 60 years of age, and this is expected to increase to 40 million as the age of the population increases, making this a public
25 health problem of enormous magnitude (Houge & Mersfelder, 2002, Ann Pharmacother., 36, 679-686; McCarthy et al., 1994, Textbook of Pain, 387-395). Most patients with osteoarthritis seek medical attention because of the associated pain. Arthritis has a significant impact on psychosocial and physical function and is known to be the leading cause of disability in later life. Ankylosing spondylitis is also a rheumatic
30 disease that causes arthritis of the spine and sacroiliac joints. It varies from intermittent episodes of back pain that occur throughout life to a severe chronic disease that attacks the spine, peripheral joints and other body organs.

Another type of inflammatory pain is visceral pain which includes pain associated with inflammatory bowel disease (IBD). Visceral pain is pain associated with the viscera,

which encompass the organs of the abdominal cavity. These organs include the sex organs, spleen and part of the digestive system. Pain associated with the viscera can be divided into digestive visceral pain and non-digestive visceral pain. Commonly encountered gastrointestinal (GI) disorders that cause pain include functional bowel disorder (FBD) and inflammatory bowel disease (IBD). These GI disorders include a wide range of disease states that are currently only moderately controlled, including, in respect of FBD, gastro-esophageal reflux, dyspepsia, irritable bowel syndrome (IBS) and functional abdominal pain syndrome (FAPS), and, in respect of IBD, Crohn's disease, ileitis and ulcerative colitis, all of which regularly produce visceral pain. Other types of visceral pain include the pain associated with dysmenorrhea, cystitis and pancreatitis and pelvic pain.

It should be noted that some types of pain have multiple aetiologies and thus can be classified in more than one area, e.g. back pain and cancer pain have both nociceptive and neuropathic components.

Other types of pain include:

- pain resulting from musculo-skeletal disorders, including myalgia, fibromyalgia, spondylitis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, dystrophinopathy, glycogenolysis, polymyositis and pyomyositis;
- heart and vascular pain, including pain caused by angina, myocardial infarction, mitral stenosis, pericarditis, Raynaud's phenomenon, scleredoma and skeletal muscle ischemia;
- head pain, such as migraine (including migraine with aura and migraine without aura), cluster headache, tension-type headache mixed headache and headache associated with vascular disorders; and
- orofacial pain, including dental pain, otic pain, burning mouth syndrome and temporomandibular myofascial pain.

Neoplasias that produce PGs include brain cancer, bone cancer, epithelial cell derived neoplasia (epithelial carcinoma) such as basal cell carcinoma, adenocarcinoma, gastrointestinal cancer such as lip cancer, mouth cancer, esophageal cancer, small bowel cancer and stomach cancer, colon cancer, liver cancer, bladder cancer, pancreatic cancer, ovarian 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 effect epithelial cells throughout the body.

The compounds of the invention can also be used to treat the fibrosis which occurs with radiation therapy and adenomatous polyps, including familial adenomatous polyposis (FAP).

A mPGES-1 inhibitor may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of pain. Such combinations offer the possibility of significant advantages, including patient compliance, ease of dosing and synergistic activity.

In the combinations that follow the compound of the invention may be administered simultaneously, sequentially or separately in combination with the other therapeutic agent or agents.

For example, the mPGES-1 inhibitor of formula (I), or a pharmaceutically acceptable salt thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

- an inhibitor of nerve growth factor signaling, such as: an agent that binds to NGF and inhibits NGF biological activity and/or downstream pathway(s) mediated by NGF signaling (e.g. tanezumab), a TrkA antagonist or a p75 antagonist;
- a sodium channel modulator, such as lidocaine; more particularly a Nav1.7 channel modulator, for example one or more compounds disclosed in WO2009/012242; an alternative sodium channel modulator, such as a Nav1.3 modulator (e.g. those disclosed in WO2008/118758); or a Nav1.8 modulator (e.g. those disclosed in WO 2008/135826, such as N-[6-Amino-5-(2-chloro-5-methoxyphenyl)pyridin-2-yl]-1-methyl-1H-pyrazole-5-carboxamide;
- a compound which increases the levels of endocannabinoid, such as a compound with fatty acid amid hydrolase inhibitory (FAAH) activity, in particular those disclosed in WO 2008/047229 (e.g. N-pyridazin-3-yl-4-(3-[[5-(trifluoromethyl)pyridine-2-yl]oxy}benzylidene)piperidine-1-carboxamide);
- an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;
- a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, meloxicam, nabumetone,

naproxen, nimesulide, nitroflurbiprofen, olsalazine, oxaprozin, phenylbutazone, piroxicam, sulfasalazine, sulindac, tolmetin or zomepirac;

- a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobarbital, secobarbital, talbutal, theamylal or thiopental;
- a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam;
- an H₁ antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine;
- a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone;
- a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphenadine;
- an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinine, cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid, budipine, EN-3231 (MorphiDex®, a combination formulation of morphine and dextromethorphan), topiramate, neramexane or perzinfotel including an NR2B antagonist, e.g. ifenprodil, traxoprodil or (–)-(R)-6-{2-[4-(3-fluorophenyl)-4-hydroxy-1-piperidinyl]-1-hydroxyethyl-3,4-dihydro-2(1H)-quinolinone};
- an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine, guanfacine, dexmetatomidine, modafinil, or 4-amino-6,7-dimethoxy-2-(5-methane-sulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;
- a tricyclic antidepressant, e.g. desipramine, imipramine, amitriptyline or nortriptyline;
- an anticonvulsant, e.g. carbamazepine, lamotrigine, topiramate or valproate;
- a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]-naphthyridine-6-13-dione (TAK-637), 5-[[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]-methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), aprepitant, lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]-methylamino]-2-phenylpiperidine (2S,3S);

- a muscarinic antagonist, e.g oxybutynin, tolterodine, propiverine, trospium chloride, darifenacin, solifenacin, temiverine and ipratropium;
- a COX-2 selective inhibitor, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib, deracoxib, etoricoxib, or lumiracoxib;
- 5 • a coal-tar analgesic, in particular paracetamol;
- a neuroleptic such as droperidol, chlorpromazine, haloperidol, perphenazine, thioridazine, mesoridazine, trifluoperazine, fluphenazine, clozapine, olanzapine, risperidone, ziprasidone, quetiapine, sertindole, aripiprazole, sonepiprazole, blonanserin, iloperidone, perospirone, raclopride, zotepine, bifeprunox, asenapine,
- 10 lurasidone, amisulpride, balaperidone, palindore, eplivanserin, osanetant, rimonabant, meclinertant, Miraxion® or sarizotan;
- a vanilloid receptor agonist (e.g. resiniferatoxin) or antagonist (e.g. capsazepine);
- a beta-adrenergic such as propranolol;
- a local anaesthetic such as mexiletine;
- 15 • a corticosteroid such as dexamethasone;
- a 5-HT receptor agonist or antagonist, particularly a 5-HT_{1B/1D} agonist such as eletriptan, sumatriptan, naratriptan, zolmitriptan or rizatriptan;
- a 5-HT_{2A} receptor antagonist such as R(+)-alpha-(2,3-dimethoxy-phenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (MDL-100907);
- 20 • a 5-HT₃ antagonist, such as ondansetron;
- a cholinergic (nicotinic) analgesic, such as ispronidine (TC-1734), (E)-N-methyl-4-(3-pyridinyl)-3-buten-1-amine (RJR-2403), (R)-5-(2-azetidylmethoxy)-2-chloropyridine (ABT-594) or nicotine;
- Tramadol®;
- 25 • a PDEV inhibitor, such as 5-[2-ethoxy-5-(4-methyl-1-piperazinyl-sulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil), (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]-pyrido[3,4-b]indole-1,4-dione (IC-351 or tadalafil), 2-[2-ethoxy-5-(4-ethyl-piperazin-1-yl-1-sulphonyl)-phenyl]-5-methyl-7-propyl-3H-imidazo[5,1-f][1,2,4]triazin-4-one (vardenafil), 5-(5-acetyl-2-butoxy-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 5-(5-acetyl-2-propoxy-3-pyridinyl)-3-ethyl-2-(1-isopropyl-3-azetidyl)-2,6-dihydro-7H-pyrazolo[4,3-
- 30 d]pyrimidin-7-one, 5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)pyridin-3-yl]-3-ethyl-

2-[2-methoxyethyl]-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-[(3-chloro-4-methoxybenzyl)amino]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]-N-(pyrimidin-2-ylmethyl)pyrimidine-5-carboxamide, 3-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-N-[2-(1-methylpyrrolidin-2-yl)ethyl]-4-propoxybenzenesulfonamide;

- an alpha-2-delta ligand such as gabapentin, pregabalin, 3-methylgabapentin, (1 α ,3 α ,5 α)(3-amino-methyl-bicyclo[3.2.0]hept-3-yl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-heptanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (2S,4S)-4-(3-chlorophenoxy)proline, (2S,4S)-4-(3-fluorobenzyl)-proline, [(1R,5R,6S)-6-(aminomethyl)bicyclo[3.2.0]hept-6-yl]acetic acid, 3-(1-aminomethyl-cyclohexylmethyl)-4H-[1,2,4]oxadiazol-5-one, C-[1-(1H-tetrazol-5-ylmethyl)-cycloheptyl]-methylamine, (3S,4S)-(1-aminomethyl-3,4-dimethyl-cyclopentyl)-acetic acid, (3S,5R)-3-aminomethyl-5-methyl-octanoic acid, (3S,5R)-3-amino-5-methyl-nonanoic acid, (3S,5R)-3-amino-5-methyl-octanoic acid, (3R,4R,5R)-3-amino-4,5-dimethyl-heptanoic acid and (3R,4R,5R)-3-amino-4,5-dimethyl-octanoic acid;
- metabotropic glutamate subtype 1 receptor (mGluR1) antagonist;
- a serotonin reuptake inhibitor such as sertraline, sertraline metabolite demethylsertraline, fluoxetine, norfluoxetine (fluoxetine desmethyl metabolite), fluvoxamine, paroxetine, citalopram, citalopram metabolite desmethylcitalopram, escitalopram, d,l-fenfluramine, femoxetine, ifoxetine, cyanodothiepin, litoxetine, dapoxetine, nefazodone, cericlamine and trazodone;
- a noradrenaline (norepinephrine) reuptake inhibitor, such as maprotiline, lofepramine, mirtazepine, oxaprotiline, fezolamine, tomoxetine, mianserin, bupropion, bupropion metabolite hydroxybupropion, nomifensine and viloxazine (Vivalan®), especially a selective noradrenaline reuptake inhibitor such as reboxetine, in particular (S,S)-reboxetine;
- a dual serotonin-noradrenaline reuptake inhibitor, such as venlafaxine, venlafaxine metabolite O-desmethylvenlafaxine, clomipramine, clomipramine metabolite desmethylclomipramine, duloxetine, milnacipran and imipramine;
- an inducible nitric oxide synthase (iNOS) inhibitor such as S-[2-[(1-iminoethyl)amino]ethyl]-L-homocysteine, S-[2-[(1-iminoethyl)amino]ethyl]-4,4-dioxo-L-cysteine, S-[2-[(1-iminoethyl)amino]ethyl]-2-methyl-L-cysteine, (2S,5Z)-2-amino-2-methyl-7-[(1-iminoethyl)amino]-5-heptenoic acid, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-

(5-thiazolyl)-butyl]thio]-5-chloro-3-pyridinecarbonitrile; 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-4-chlorobenzonitrile, (2S,4R)-2-amino-4-[[2-chloro-5-(trifluoromethyl)phenyl]thio]-5-thiazolebutanol, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl) butyl]thio]-6-(trifluoromethyl)-3-pyridinecarbonitrile, 2-[[[(1R,3S)-3-amino-4-hydroxy-1-(5-thiazolyl)butyl]thio]-5-chlorobenzonitrile, N-[4-[2-(3-chlorobenzylamino)ethyl]phenyl]thiophene-2-carboxamide, or guanidinoethyldisulfide;

- an acetylcholinesterase inhibitor such as donepezil;
- a prostaglandin E₂ subtype 4 (EP4) antagonist such as *N*-[({2-[4-(2-ethyl-4,6-dimethyl-1H-imidazo[4,5-c]pyridin-1-yl)phenyl]ethyl}amino)-carbonyl]-4-methylbenzenesulfonamide or 4-[(1S)-1-({[5-chloro-2-(3-fluorophenoxy)pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid; or
- a leukotriene B₄ antagonist; such as 1-(3-biphenyl-4-ylmethyl-4-hydroxy-chroman-7-yl)-cyclopentanecarboxylic acid (CP-105696), 5-[2-(2-Carboxyethyl)-3-[6-(4-methoxyphenyl)-5E-hexenyl]oxyphenoxy]-valeric acid (ONO-4057) or DPC-11870,
- a 5-lipoxygenase inhibitor, such as zileuton, 6-[(3-fluoro-5-[4-methoxy-3,4,5,6-tetrahydro-2H-pyran-4-yl])phenoxy-methyl]-1-methyl-2-quinolone (ZD-2138), or 2,3,5-trimethyl-6-(3-pyridylmethyl),1,4-benzoquinone (CV-6504).

There is also included within the scope the present invention combinations of a compound of the invention together with one or more additional therapeutic agents which slow down the rate of metabolism of the compound of the invention, thereby leading to increased exposure in patients. Increasing the exposure in such a manner is known as boosting. This has the benefit of increasing the efficacy of the compound of the invention or reducing the dose required to achieve the same efficacy as an unboosted dose. The metabolism of the compounds of the invention includes oxidative processes carried out by P450 (CYP450) enzymes, particularly CYP 3A4 and conjugation by UDP glucuronosyl transferase and sulphating enzymes. Thus, among the agents that may be used to increase the exposure of a patient to a compound of the present invention are those that can act as inhibitors of at least one isoform of the cytochrome P450 (CYP450) enzymes. The isoforms of CYP450 that may be beneficially inhibited include, but are not limited to, CYP1A2, CYP2D6, CYP2C9, CYP2C19 and CYP3A4. Suitable agents that may be used to inhibit CYP 3A4 include ritonavir, saquinavir, ketoconazole, N-(3,4-difluorobenzyl)-N-methyl-2-[(4-

methoxypyridin-3-yl)amino]sulfonyl}benzamide and N-(1-(2-(5-(4-fluorobenzyl)-3-(pyridin-4-yl)-1H-pyrazol-1-yl)acetyl)piperidin-4-yl)methanesulfonamide.

It is within the scope of the invention that two or more pharmaceutical compositions, at least one of which contains a compound of the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions. Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like. The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

In another aspect the invention provides a pharmaceutical product (such as in the form of a kit) comprising a compound of the invention together with one or more additional therapeutically active agents as a combined preparation for simultaneous, separate or sequential use in the treatment of a disorder for which a mPGES-1 inhibitor is indicated.

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment.

The invention is illustrated by the following non-limiting examples in which the following abbreviations and definitions may be used:

25	br	Broad
	δ	Chemical shift
	d	Doublet
	DCM	Dichloromethane
	DMF	Dimethylformamide
30	dd	Doublet of doublets
	DMSO	Dimethylsulfoxide
	EtOAc	Ethylacetate
	ES+	Electrospray ionisation positive scan
	ES-MS	Electrospray – Mass Spectrometry

¹ H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
HPLC	High performance liquid chromatography
LC-MS	Liquid Chromatography – Mass Spectrometry
LRMS	Low Resolution Mass Spectroscopy
5 m	Multiplet
m/z	Mass spectrum peak
q	Quartet
s	Singlet
t	Triplet

10 In the Examples that follow, the ability of the compounds of the invention to inhibit mPGES-1 was assessed according to the following human mPGES-1 enzyme assay and the ensuing IC₅₀'s are expressed as mM values.

Cloning, expression and preparation of mPGES-1

15 A 465 base pair cDNA encoding human mPGES-1 was amplified by polymerase chain reaction from an in-house library of human testis DNA. The oligonucleotide primers incorporated NcoI and EcoRI restriction sites 5' and 3' of the coding region, respectively, which were used to clone the cDNA into the pENTR4 vector from Invitrogen. This entry clone was recombined with pDEST10, which supplies an N-
20 terminal His6 tag. The resultant plasmid, called pMON72365, was used to transform DH10Bac cells and generate recombinant baculoviral DNA, following manufacturer's protocols.

Sf9 insect cells were transfected with the baculoviral DNA containing mPGES-1 using Cellfectin® reagent and standard protocol. After 3-5 days, the supernatant
25 medium contained infectious recombinant virus particles capable of expressing mPGES-1. A larger stock of this virus was prepared by infecting fresh Sf9 cells, titered, and then used for protein expression. Conditions for expression were determined by a small scale optimization study followed by Western analysis of expressed protein using Cayman (Ann Arbor, MI) anti- mPGES-1 Ab (data not shown). For expression, Sf9 cells
30 were seeded at 1 x 10⁶ cells/mL and infected with virus at a multiplicity of infection of 0.1. At 48 hours post-infection, the cells were harvested, and the pellets stored at -80°C.

Cells were suspended in 10 x (w/v) PBS and sonicated for 20 seconds with a medium tip. Cell debris was removed by centrifugation @ 10,000 x g for 20 minutes.

The resulting supernatant was aliquoted and frozen @ -80°C for use in the assay. The enzyme was tittered to produce conversion of approximately 20% of the substrate during a 41 second reaction.

5 *mPGES-1 ELISA assay*

Production of PGE₂ by mPGES-1 was assessed by incubation of enzyme with 2 uM PGH₂ for 41 seconds at room temperature and assessment of PGE₂ by Enzyme Linked Immunosorbant Assay (ELISA). Enzyme is suspended in assay buffer comprised of 100 mM KPO₄ pH 6.2 (stock pH), 2.5 mM glutathione at a dilution that
10 produces approximately 100-150 ng/ml PGE₂ (approximately 15 to 20% conversion of substrate to product), typically about 400-800x. Compound solubilized in DMSO and added at a 1:9 w/w DMSO to enzyme ratio. PGH₂ (Cayman Chemical, Ann Arbor MI) is diluted 12.8 x in ice cold 10 mM HCl from a 278 uM stock in acetone. The reaction is begun by the addition of 1:10 volume of PGH₂ to the enzyme inhibitor mixture for a final
15 concentration of 2 uM. The reaction is terminated by the addition of 1:10 volumes of 2.5 mM FeCl₂ (Final concentration, a 25 mM stock FeCl₂ is made-up fresh in 50 mM citric acid and sonicated). The reaction is immediately diluted 120 x into ELISA buffer (according to Cayman Chemical, Ann Arbor MI recipe). PGE₂ formed was calculated from a standard curve of PGE₂ by ELISA (Cayman Chemical, Ann Arbor MI). The %
20 control activity was calculated as the percentage difference between negative control (100% inhibited with a reference compound) and enzyme only control. The difference between enzymatic vs. non-enzymatic production of PGE₂ are typically 3-4 fold. IC₅₀'s are calculated by 4 parameter log fit of the % control data.

The compound of formula (I) was tested in a beagle whole blood assay at 7 drug
25 concentrations. A 96 well plate was used for the mPGEs1 assay (ELISA plate). Blood was drawn from 1 batch of three dogs, from which mPGES1 assay was developed for the compound of formula (I). The compound was dispensed into 3 columns on a Blood plate for each animal. 3 columns are no drug controls with one of these also being a no LPS control (columns 4, 11 and 12, respectively). Plasma drawn from the blood plates
30 are then diluted and transferred to 3 ELISA plates, with compounds randomized to two locations (columns 4-6 and 8-10) on an ELISA plate.

Plasma or Serum Analysis of mPGES1 (in vitro): All samples were thawed and then assayed together on the same day. mPGES1 inhibitions were determined using EIA kits from Cayman Chemical. Prostaglandin E₂ (PGE₂) was used to determine the activity of

COX-2. (Samples of the positive control plasma were assayed in a preliminary ELISA assay to determine the best dilution for each animal. Using the EIA kit buffer, several dilutions are made; (tested at 1:100, 1:500, 1:1000 and 1:2000). The primary ELISA assay is performed using the best dilution factor for each animal. Both EIA's were performed according to the protocol provided with the kits. Test results were read using Molecular Devices Spectramax 340 PC spectrophotometer and Softmax Pro 5.0 software. GraphPad Prism 5.0 was used to generate non-linear regression curves (sigmoidal dose response-variable slope) and obtain IC₅₀ values and 95% Confidence Limits.

RESULT

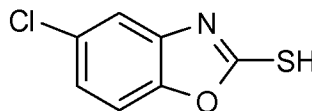
The mPGES-1 inhibitor of the compound of formula (I) showed an IC₅₀ value of 90 nM and an IC₉₀ value of close to 1 uM when measuring inhibition of PGE₂ production.

Example preparation of 1-[5-chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]-N-[(1S,3S)-3-(hydroxymethyl)cyclohexyl]piperidine-4-carboxamide

Step 1: Preparation of 2-chloro-2-aminophenol

To the 3-chlorophenol (1 equivalent, commercially available) in glacial acetic acid (1 mL/mmol) is added dropwise conc nitric acid (1.2 equivalents) in glacial acetic acid (1 mL/mmol). The contents are stirred for one hour and poured onto ice water. After stirring one hour, the solid is filtered to give the 4-chloro-2-nitrophenol. The 4-chloro-2-nitrophenol (1.0 equivalents), platinum (sulfided, 5% wt on carbon, reduced, dry, 4-5% weight) and methanol are stirred at 55 psi hydrogen overnight. The mixture is filtered through diatomaceous earth and the filtrate is concentrated *in-vacuo* to give the title compound.

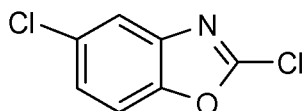
Step 2: Preparation of 5-chloro-1,3-benzoxazole-2-thiol



4-Chloro-2-aminophenol (11.7.0 g, 81.5 mmol), potassium O-ethylcarbonodithioate (14.3, 81.5 mmol) and pyridine (105 mL) were heated to reflux with condenser vented to bleach trap for 30 minutes. The reaction was cooled to room temperature and poured into a flask containing concentrated HCl (39 mL) and ice water (250 mL). The mixture

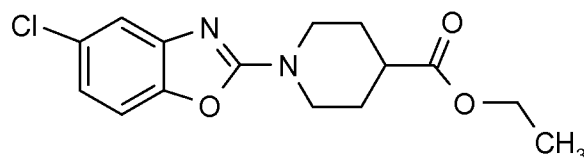
was stirred for 5 minutes, then filtered off and washed with H₂O (40 mL). The solid was dissolved in EtOAc (250 mL) and washed with HCl (1N, 15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated to collect the title compound as a solid.

5 Step 3: Preparation of 2,5-dichloro-1,3-benzoxazole.



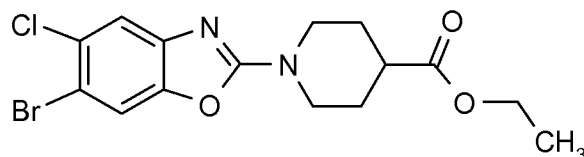
5-chloro-1,3-benzoxazole-2-thiol (8.09 g, 43.6 mmol) dissolved in CHCl₃ (65 mL) and stirred at ice bath for 10 minutes. Chlorine gas was bubbled into the solution for 10 minutes. The reaction mixture was further stirred at room temperature overnight. The reaction mixture was poured into ice water (70 mL) and extracted with aq. 2N NaOH (30mLx2), then ice water (30mL). The CHCl₃ solution was allowed to stand for 10 minutes, then filtered through a plug of silica gel to give clear solution. The solvent was removed under reduced pressure to afford semi-oil crude product. The crude product was dissolved in CHCl₃ (25 mL) and filtered through diatomaceous earth. The solvent was removed under reduced pressure to give the title compound as a solid.

Step 4: Preparation of ethyl 1-(5-chloro-1,3-benzoxazol-2-yl)piperidine-4-carboxylate.



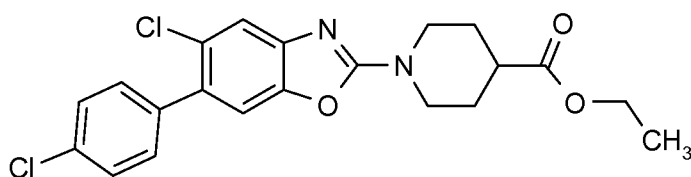
To 2,5-dichloro-1,3-benzoxazole (2.5 gm 13.5 mmol) in dichloromethane (46 mL) was added triethylamine (3.5 gm, 13.5 mmol) and ethyl isonipecotatate (2.11 gm, 13.5 mmol) with stirring at room temperature overnight. The organic layer was washed with aq. 1N NaHCO₃ (20 mL). The aqueous layer was extracted with CH₂Cl₂ (15 mL). The organic layers were combined, dried over Na₂SO₄ and removed under reduced pressure to give the title compound as a solid.

Step 5: Preparation of Ethyl 1-(6-bromo-5-chloro-1,3-benzoxazol-2-yl)piperidine-4-carboxylate



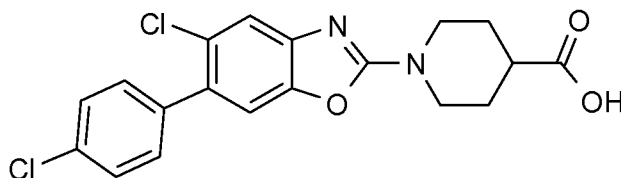
Ethyl 1-(5-chloro-1,3-benzoxazol-2-yl)piperidine-4-carboxylate (2050 mg, 6.639 mmol) was dissolved into acetic acid (30 mL) followed by the addition of bromine (1.06 g, 6.6 mmol). The solution was allowed to stir for 1 hour at room temperature. The resulting solution was concentrated *in-vacuo*. The residue was filtered through a pad of silica gel, eluting with EtOAc/hexanes (10 – 25%) to give the title compound as a white solid. ES-MS *m/z* 388 (M+H).

Step 6: Preparation of ethyl 1-[5-chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]piperidine-4-carboxylate



Ethyl 1-(6-bromo-5-chloro-1,3-benzoxazol-2-yl)piperidine-4-carboxylate (1000 mg, 2.58 mmol) was dissolved into 1,2-dimethoxyethane (5 mL) followed by the addition of tetrakis(triphenylphosphine) palladium(0) (149 mg, 0.129 mmol), (4-chlorophenyl)boronic acid (403 mg, 2.258 mmol) and cesium carbonate 2M (2.58 mL, 5.16 mmol). The solution was heated to 80°C overnight. The resulting solution was poured over a pad of diatomaceous earth and concentrated *in-vacuo*. The residue was filtered through a pad of silica gel, eluting with EtOAc/hexanes (10-25%) to give the title compound as off a solid. ES-MS *m/z* 419 (M+H).

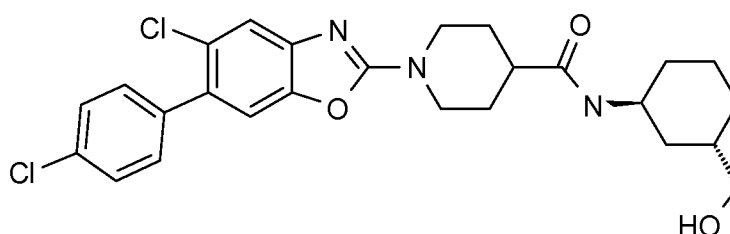
Step 7: Preparation of 1-[5-Chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]piperidine-4-carboxylic acid



Ethyl 1-[5-chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]piperidine-4-carboxylate (800 mg, 1.91 mmol), 2.5 N sodium hydroxide (0.763 mL, 1.91 mmol), methanol (5 mL) and water (1 mL) were stirred overnight. Contents were concentrated *in-vacuo* to remove the methanol and the remaining solution was made acidic with 10% aqueous HCl.

5 Contents were filtered to give the title compound as a white solid. ES-MS m/z 391 (M+H).

Step 8: Preparation of 1-[5-Chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]-N-[(1S,3S)-3-(hydroxymethyl)cyclohexyl]piperidine-4-carboxamide



10

To 1-[5-chloro-6-(4-chlorophenyl)-1,3-benzoxazol-2-yl]piperidine-4-carboxylic acid (492 mg, 1.26 mmol) in DMF (10 mL) was added (1S,3S)-3-hydroxymethylcyclohexylamine (195 mg, 1.5 mmol). Added triethylamine (0.54 mL, 3.77 mmol), stirred 15 minutes and then added HBTU (716 mg, 1.89 mmol) and stirred overnight. Added water and filtered to collect a solid. The solid was dissolved in EtOAc and filtered through a small plug of silica gel, eluting with EtOAc to give a white solid. Triturated with EtOAc/heptanes and filtered to give the title compound.

15

M+H calc 502.1664; found 502.1743.

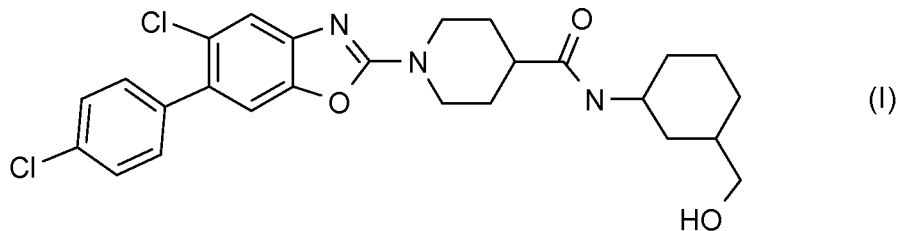
¹H NMR (400 MHz, METHANOL-*d*₄) δ 1.16 - 1.29 (m, 1 H), 1.38 - 1.48 (m, 1 H), 1.55 - 1.62 (m, 4 H), 1.64 - 1.73 (m, 2 H), 1.75 - 1.92 (m, 5 H), 2.50 - 2.63 (m, 1 H), 3.16 - 3.27 (m, 2 H), 3.44 (d, $J=6.83$ Hz, 2 H), 3.96 - 4.03 (m, 1 H), 4.26 - 4.35 (m, 2 H), 7.32 (s, 1 H), 7.35 (s, 1 H), 7.38 - 7.46 (m, 4 H).

20

CLAIMS

What is claimed is:

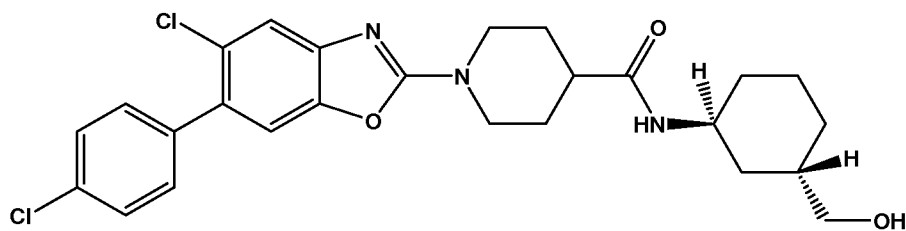
1. A compound of formula (I):



5

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 which is



10

or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition comprising a compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable excipients.
4. A pharmaceutical composition according to claim 3 further comprising one or more additional therapeutic agents.
5. A compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

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6. A compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof for use in the treatment of a disorder for which a mPGES-1 inhibitor is indicated.
- 5 7. A compound for use according to claim 6 wherein the disorder for which a mPGES-1 inhibitor is indicated is pain.
8. A compound for use according to claim 7 wherein the pain is inflammatory pain.
- 10 9. Use of a compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of a disorder for which a mPGES-1 inhibitor is indicated.
- 15 10. A method of treating a disorder in an animal for which a mPGES-1 inhibitor is indicated, comprising administering to said animal a therapeutically effective amount of a compound of formula (I) of claim 1 or a pharmaceutically acceptable salt thereof.
- 20 11. The method of claim 10 wherein the disorder for which a mPGES-1 inhibitor is indicated is pain.
12. The method of claim 11 wherein the disorder for which a mPGES-1 inhibitor is indicated is inflammatory pain.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/055736

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/04 A61K31/454 A61P29/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/084218 A1 (BOEHRINGER INGELHEIM INT [DE]; BIOLIPOX AB [SE]; HAUER NORBERT [DE]; A) 17 July 2008 (2008-07-17) cited in the application claims 1-23	1-12
A	WO 2008/071944 A1 (BOEHRINGER INGELHEIM INT [DE]; BIOLIPOX AB [SE]; PELCMAN BENJAMIN [SE]) 19 June 2008 (2008-06-19) claims 1-43	1-12



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

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

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

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

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

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

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Marzi, Elena

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Information on patent family members

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