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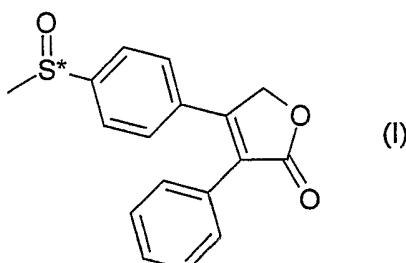
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(54) Title: 3-PHENYLFURAN-2-ONE DERIVATIVES AS COX-2 INHIBITOR



(57) Abstract: The present invention relates to 3-phenylfuran-2-ones of formula (I), processes for their preparation, pharmaceutical compositions containing them, and their medical uses.

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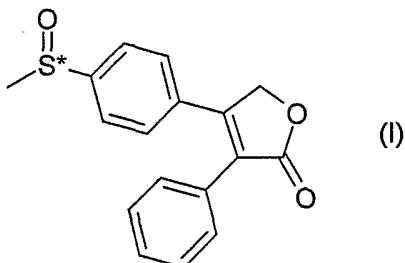
## 3-PHENYLFURAN-2-ONE DERIVATIVE AS COX-2 INHIBITOR

This invention relates to a new therapeutically useful 3-phenylfuran-2-one, to processes for their preparation, to pharmaceutical compositions containing them and to 5 their use as medicaments.

It is known that non-selective inhibition of the enzyme cyclooxygenase (COX) prevents the overproduction of prostaglandins associated with inflammation, which are mediated by cyclooxygenase-2 (COX-2) but, at the same time, deprives tissues of basal 10 levels of prostaglandins necessary for the health of certain tissues mediated largely by cyclooxygenase-1 (COX-1). Non steroidal anti-inflammatory drugs are non-selective inhibitors of COX and for that reason, have side effects of decreased renal blood flow, decreased platelet function, dyspepsia and gastric ulceration.

15 We have now found that certain 3-phenylfuran-2-ones selectively inhibit COX-2 in preference to COX-1 and are useful in the treatment of COX-2 mediated diseases and their symptoms, such as inflammation, pain, fever, and asthma, with fewer side effects.

Accordingly, the present invention provides a novel compound of formula (I)



20

The compounds of formula (I) have a chiral center at the sulfur atom of the sulfinyl group, shown by an asterisk (\*) in the formula, and consequently exist in the form of two different enantiomers. The two enantiomers and mixtures thereof including racemic 25 mixtures are encompassed by the present invention. References to a compound of formula (I) in this specification, including the accompanying claims, unless otherwise specified, embrace each of the enantiomers and racemic and scalemic mixtures of the two enantiomers.

Other aspects of the present invention are: a) a process for the preparation of the compounds; b) pharmaceutical compositions comprising an effective amount of said compounds; c) the use of said compounds in the manufacture of a medicament for the treatment of diseases susceptible to amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2); and d) methods of treatment of diseases susceptible to amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2), which methods comprise the administration of the compounds of the invention to a subject in need of treatment.

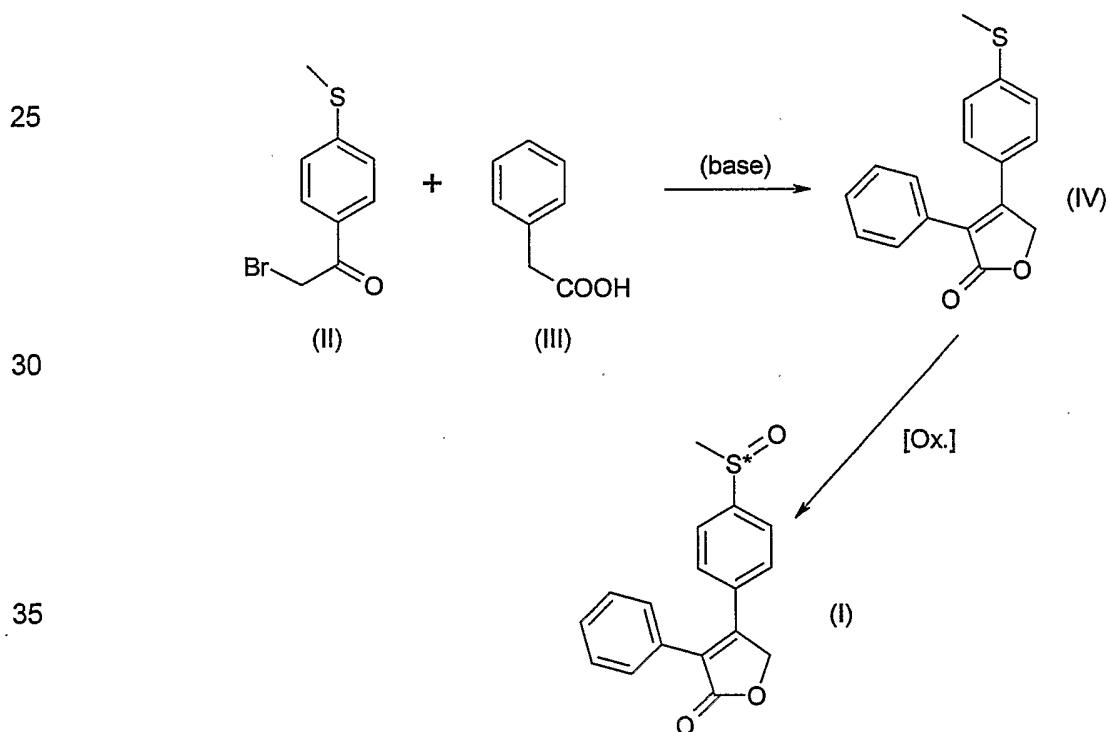
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10 Particular individual compounds of the invention are:

(R) 4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one  
 (S) 4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one

15 In another aspect the present invention encompasses a synthetic process for the preparation of the compounds of formula (I) which is depicted in Scheme 1 and involves the reaction of 2-bromo-1-[4-(methylthio)phenyl]ethanone (II) with phenylacetic acid (III) in the presence of a base to yield 4-[4-(methylthio)phenyl]-3-phenylfuran-2(5H)-one (IV) which is isolated and then oxidised to 4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one 20 (I).

SCHEME 1



Following scheme (I) phenylacetic acid and a mixture of a base (e.g. potassium carbonate) and a crown ether are added to a suspension of 2-bromo-1-[4-(methylthio)phenyl]ethanone in a solvent (e.g. acetonitrile). The mixture is stirred at room temperature for 1 hour and 2 hours at reflux. After removal of the solvent, dichloromethane (400 ml) and saturated ammonium chloride (300 ml) are added to the residue. The organic layer is washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give a residue, which was further purified to yield 4-[4-(Methylthio)phenyl]-3-phenylfuran-2(5H)-one.

According to the invention the compound of formula (I) is prepared by reaction of a compound of formula (IV) with an oxidising agent. The oxidation step can be made under non-stereo specific conditions or under stereo specific conditions. The oxidizing agent is preferably sodium metaperiodate when it is desired to obtain racemic mixtures of compounds or a mixture of titanium tetrakisopropoxide, t-butyl hydroperoxide and either the (R, R) or the (S, S) forms of diethyl tartrate when it is desired to obtain mixtures of compounds of formula (I) enriched with compounds having a specific configuration at the sulfinyl chiral center. The reaction between the mercapto derivative of formula (IV) and the oxidising agent is preferably carried out in an organic solvent, preferably a chlorinated solvent or a mixture of chlorinated solvents and  $\text{C}_1\text{-C}_4$  alcohols at a temperature of from -25°C to 40°C. It is preferred that the chlorinated solvent is selected from the group consisting of 1,2-dichloroethane, methylene chloride, chloroform and mixtures thereof. The  $\text{C}_1\text{-C}_4$  alcohol is preferably selected from methanol and ethanol. Preferred solvent systems are 1,2-dichloromethane or a mixture of methylene chloride with methanol or ethanol.

In the first case the mercapto compound of the previous step is dissolved in methanol and a solution of sodium metaperiodate is added dropwise at 0°C and this mixture is stirred at this temperature for 2 hours and 3 days at room temperature. Then, the reaction mixture is poured into water, extracted with ethyl acetate, the organic solution washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure. The residue, chromatographically purified, yields 4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (2.27 g, 81%) as an off-white solid.

In the second case *t*-butyl hydroperoxide in nonane and the mercapto compound of the previous step are added successively to a stirred solution of titanium tetraisopropoxide and an optically active diethyl tartrate (either the (R,R) or the (S,S) enantiomers) in dry 5 1,2-dichloroethane cooled to -20°C. The mixture is stirred at -20°C for 5 h, then washed with a 5% aqueous solution of sodium sulfite (50 ml) and brine. The organic layer is dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. The residue after purification by flash chromatography yields an optically pure enantiomer of 4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one obtained as an off-white solid.

10

## PHARMACOLOGICAL ACTIVITY

The following biological tests and data further illustrate this invention.

15

### COX-1 and COX-2 activities in human whole blood

Fresh blood from healthy volunteers who had not taken any non-steroidal anti-inflammatory drugs for at least 7 days prior to blood extraction was collected in heparinized tubes (20 units of heparin per ml). For the COX-1 activity determination, 500 20 µl aliquots of blood were incubated with either 5 µl vehicle (dimethylsulphoxide) or 5 µl of a test compound solution for 24 h at 37°C. Calcium ionophore A23187 (25 µM) was added 20 min before the incubation was ended. Plasma was separated by centrifugation (10 min at 13000 rpm) and kept at -30°C until TXB<sub>2</sub> levels were measured using an enzyme immunoassay kit (ELISA).

25

The effect of the compounds was evaluated by incubating each compound at five to six different concentrations with triplicate determinations. IC<sub>50</sub> values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer.

30

For the COX-2 activity determination, 500 µl aliquots of blood were incubated in the presence of LPS (10 µg/ml) for 24 h at 37°C in order to induce the COX-2 expression (Patriagnani et al., J. Pharm. Exper. Ther. 271; 1705-1712 (1994)). Plasma was separated by centrifugation (10 min at 13000 rpm) and kept at -30°C until PGE<sub>2</sub> levels were measured using an enzyme immunoassay kit (ELISA). The effects of inhibitors were 35 studied by incubating each compound (5 µl aliquots) at five to six different concentrations

with triplicate determinations in the presence of LPS for 24 hours. IC<sub>50</sub> values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer.

The results obtained from the biological assays are shown in Table 1 which shows the

5 inhibition of COX-1 and COX-2 obtained with the racemic mixture of 4-[4-(methylsulfinyl)-phenyl]-3-phenylfuran-2(5H)-one.

**TABLE I**

Example	COX-1 IC <sub>50</sub> μM	COX-2 IC <sub>50</sub> μM	Ratio COX-1/COX-2
4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (racemate)	33,4	4,93	6,8
4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (Enantiomer 1a)	32,2	4,22	7,6
4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (Enantiomer 1b)	37,8	2,10	18

10 As shown in Table 1, the 3-phenylfuran-2-ones (I) are potent and selective COX-2 inhibitors. Thus the compounds of the invention are preferably selective inhibitors of mammalian COX-2, for example human COX-2.

15 The compounds of the invention also preferably have low inhibitory activity toward mammalian COX-1, for example human COX-1. Inhibitory activity can typically be measured by *in vitro* assays, for example as described above. The compounds of the present invention have also shown an unexpected pharmacokinetic profile.

20 Preferred compounds of the invention have an IC<sub>50</sub> value for COX-2 of less than 50μM, preferably less than 10μM more preferably less than 5μM. Preferred compounds of the invention also have an IC<sub>50</sub> value for COX-1 of greater than 10μM, preferably

greater than 20 $\mu$ M. As an indicator of selectivity for inhibition of COX-2 over COX-1, the ratio of COX-1/COX-2 IC<sub>50</sub> values is preferably greater than 10.

The present invention further provides a compound of formula (I) for use in a  
5 method of treatment of the human or animal body by therapy, in particular for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention or treatment of colorectal cancer or neurodegenerative diseases, for example, Alzheimer's disease.

10 The present invention further provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment of pain, fever or inflammation, to inhibit prostanoid-induced smooth muscle contraction or for the prevention or treatment of colorectal cancer.

15 The compounds of formula (I) are useful for relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhoea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, bursitis, tendinitis, injuries, following surgical and dental procedures and arthritis including rheumatoid arthritis,  
20 osteoarthritis, gouty arthritis, spondyloarthropathies, systemic lupus erythematosus and juvenile arthritis. They may also be used in the treatment of skin inflammation disorders such as psoriasis, eczema, burning and dermatitis. In addition, such compounds may be used for the prevention or treatment of colorectal cancer or neurodegenerative diseases, for example, Alzheimer's disease.

25 The compounds of formula (I) will also inhibit prostanoid-induced smooth muscle contraction and therefore may be used in the treatment of dysmenorrhoea, premature labour, asthma and bronchitis.

30 The compounds of formula (I) can be used as alternative to conventional non-steroidal anti-inflammatory drugs, particularly where such non-steroidal anti-inflammatory drugs may be contraindicated such as the treatment of patients with gastrointestinal disorders including peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis, Crohn's disease, inflammatory bowel syndrome and irritable bowel syndrome,  
35 gastrointestinal bleeding and coagulation disorders, kidney disease (e.g. impaired renal

function), patients prior to surgery or taking anticoagulants, and patients susceptible to non-steroidal anti-inflammatory drugs induced asthma.

The compounds can further be used to treat inflammation in diseases such as  
5 vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anaemia, Hodgkin's disease, scleroderma, type I diabetes, myasthenia gravis, sarcoidosis, nephrotic syndrome, Behcet's syndrome, polymyositis, hypersensitivity, conjunctivitis, gingivitis and myocardial ischaemia.

10 Compounds of the present invention are inhibitors of cyclooxygenase-2 enzyme and are thereby useful to treat the cyclooxygenase-2 mediated diseases enumerated above.

Accordingly, the compounds of the present invention and pharmaceutical  
15 compositions comprising such compounds may be used in a method of treatment of disorders of the human body which comprises administering to a patient requiring such treatment an effective amount of such compounds.

The present invention also provides pharmaceutical compositions, which  
20 comprise, as an active ingredient, at least a compound of formula (I) in association with a pharmaceutically acceptable excipient such as a carrier or diluent. The active ingredient may comprise 0.001% to 99% by weight, preferably 0.01% to 90% by weight of the composition depending upon the nature of the formulation and whether further dilution is to be made prior to application.

25 Preferably the compositions are made up in a form suitable for oral, topical, nasal, inhalation, rectal, percutaneous or injectable administration.

The pharmaceutically acceptable excipients that are admixed with the active  
30 compound, to form the compositions of this invention are well known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

35 Compositions of this invention are preferably adapted for injectable and per os administration. In this case, the compositions for oral administration may take the form of

tablets, retard tablets, sublingual tablets, capsules or liquid preparations, such as mixtures, elixirs, syrups or suspensions, all containing the compound of the invention; such preparations may be made by methods well-known in the art.

5 The diluents that may be used in the preparation of the compositions include those liquid and solid diluents that are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or capsules may conveniently contain between 2 mg and 500 mg of active ingredient.

10 The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of the active compound in association with, for example, sucrose to form a syrup. The suspensions may comprise an insoluble active compound of the invention in association with water, together with a suspending agent or flavouring agent.

15 Compositions for parenteral injection may be prepared from the compounds of the present invention which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

20 Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

25 The invention is illustrated by the following Preparation and Examples, which do not limit the scope of the invention in any way.

1H Nuclear Magnetic Resonance Spectra were recorded on a Varian Gemini 300 spectrometer. Melting points were recorded using a Perkin Elmer DSC-7 apparatus. Optical rotations were determined on a Perkin Elmer 241MC Polarimeter. Enantiomeric 30 purities were determined by capillary electrophoresis on an Agilent 3D (Agilent Technologies, Waldbronn, Germany), using a diode array detector and a capillary of melted silica (56 cm longitude, 50 micron internal diameter). The conditions used were the following: buffer (phosphoric acid 20 mM adjusted to pH 3.0 with triethanolamine, sulphobutylether cyclodextrin of substitution grade 7 (SBE-7CD), 10% acetonitrile);

voltage (30 kV with negative polarity); temperature (20°C); wavelength (200 nm (15 nm bandwidth) with a reference of 400 nm (80 nm bandwidth)).

**EXAMPLES:**

5

**PREPARATION 1**

**4-[4-(Methylthio)phenyl]-3-phenylfuran-2(5H)-one**

To a suspension of 2-bromo-1-[4-(methylthio)phenyl]ethanone (3.18 g, 13 mmol) in acetonitrile (70 ml) was added phenylacetic acid (1.77 g), 18-crown-6 (0.014 g) and 10 potassium carbonate (3.22 g). The mixture was stirred at room temperature for 1 hour and 2 hours at reflux. Then, the solvent was removed under reduced pressure and dichloromethane (400 ml) and saturated ammonium chloride (300 ml) were added to the residue. The organic layer was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to give a residue, which was purified by flash chromatography 15 eluting with dichloromethane. 4-[4-(Methylthio)phenyl]-3-phenylfuran-2(5H)-one was obtained (2.31 g, 63%) as an orange solid.

$\delta$  (DMSO): 2.47 (s, 3H), 5.38 (s, 2H), 7.23-7.45 (m, 9H).

**EXAMPLE 1**

**20 4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one**

To a solution of the title compound of Preparation 1 (1.80 g, 6.4 mmol) in methanol (31 ml) was added dropwise a solution of sodium metaperiodate (1.36 g) in water (15 ml) at 0°C and this mixture was stirred at this temperature for 2 hours and 3 days at r.t. Then, the reaction was poured into water, extracted with ethyl acetate (3 x 100 ml), the organic 25 solution washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent removed under reduced pressure. The residue was purified by flash chromatography and dichloromethane/ethyl acetate/ethanol/acetic acid (78/17/3/2) as eluent. 4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (2.27 g, 81%) was obtained as an off-white solid.

m.p.: 149-150°C

30  $\delta$  (DMSO): 2.76 (s, 3H), 5.42 (s, 2H), 7.33-7.45 (m, 5H), 7.55 (d,  $J=8.4$  Hz, 2H), 7.71 (d,  $J=8.4$  Hz, 2H).

**EXAMPLE 2**

**(R)-4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (Enantiomer 1a)**

To a stirred solution of titanium tetraisopropoxide (1.05 ml, 3.5 mmol) and (R,R)-diethyl tartrate (2.45 ml, 14.2 mmol) in dry 1,2-dichloroethane (25 ml) cooled to -20°C were added successively *t*-butyl hydroperoxide 5.5 M in nonane (1.29 ml, 7.1 mmol) and the title compound of Preparation 1 (1.0 g, 3.5 mmol). The mixture was stirred at -20°C for 5 h, then washed with a 5% aqueous solution of sodium sulfite (50 ml) and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. The residue was purified by flash chromatography and ethyl acetate/methanol (95/5) as eluent. 4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (0.48 g, 45%, 100% ee) in the form of enantiomer 1a was obtained as an off-white solid.

5 [α]<sub>D</sub><sup>22</sup> = +93.1 (c 0.25, MeOH)  
m.p.: 149-150°C  
δ (DMSO): 2.76 (s, 3H), 5.42 (s, 2H), 7.33-7.45 (m, 5H), 7.55 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H).

15 EXAMPLE 3

**(S)-4-[4-(Methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one (Enantiomer 1b)**  
Obtained in the form of enantiomer 1b as an off-white solid (63%, 93.4% ee) from the title compound of Preparation 1 and (S,S)-diethyl tartrate by the procedure described in Example 2.

20 [α]<sub>D</sub><sup>22</sup> = -82.3 (c 0.25, MeOH)  
m.p.: 149-150°C  
δ (DMSO): 2.76 (s, 3H), 5.42 (s, 2H), 7.33-7.45 (m, 5H), 7.55 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H).

25 COMPOSITION EXAMPLES:

COMPOSITION EXAMPLE 1

**Preparation of tablets**

Formulation:

30 Compound of the present invention 5.0 mg  
Lactose 113.6 mg  
Microcrystalline cellulose 28.4 mg  
Light silicic anhydride 1.5 mg  
Magnesium stearate 1.5 mg

Using a mixer machine, 15 g of the compound of the present invention are mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture is subjected to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material is pulverised using a hammer mill, and the pulverised 5 material is screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate are added to the screened material and mixed. The mixed product is subjected to a tablet making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

## 10 COMPOSITION EXAMPLE 2

### **Preparation of coated tablets**

Formulation:

Compound of the present invention	5.0 mg
Lactose	95.2 mg
15 Corn starch	40.8 mg
Polyvinylpyrrolidone K25	7.5 mg
Magnesium stearate	1.5 mg
Hydroxypropylcellulose	2.3 mg
Polyethylene glycol 6000	0.4 mg
20 Titanium dioxide	1.1 mg
Purified talc	0.7 mg

Using a fluidised bed granulating machine, 15 g of the compound of the present invention are mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of 25 polyvinylpyrrolidone is dissolved in 127.5 g of water to prepare a binding solution. Using a fluidised bed granulating machine, the binding solution is sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate is added to the obtained granulates and mixed. The obtained mixture is subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 30 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution is prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above are

coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

### COMPOSITION EXAMPLE 3

#### 5 Preparation of capsules

Formulation:

Compound of the present invention	5.0 mg
Lactose monohydrate	200 mg
Colloidal silicon dioxide	2 mg
10 Corn starch	20 mg
Magnesium stearate	4 mg

25 g of active compound, 1 Kg of lactose monohydrate, 10 g of colloidal silicon dioxide, 100 g of corn starch and 20 g of magnesium stearate are mixed. The mixture is sieved 15 through a 60 mesh sieve, and then filled into 5,000 gelatine capsules.

### COMPOSITION EXAMPLE 4

#### Preparation of a cream

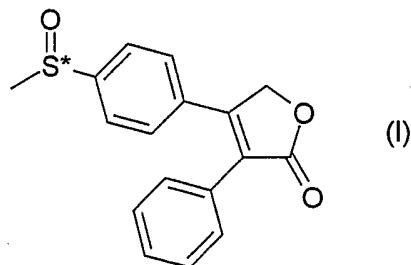
Formulation:

20 Compound of the present invention	1 %
Cetyl alcohol	3 %
Stearyl alcohol	4 %
Gliceryl monostearate	4 %
Sorbitan monostearate	0.8 %
25 Sorbitan monostearate POE	0.8 %
Liquid vaseline	5 %
Methylparaben	0.18 %
Propylparaben	0.02 %
Glycerine	15 %
30 Purified water csp.	100 %

An oil-in-water emulsion cream is prepared with the ingredients listed above, using conventional methods.

CLAIMS:

1. A compound of formula (I):



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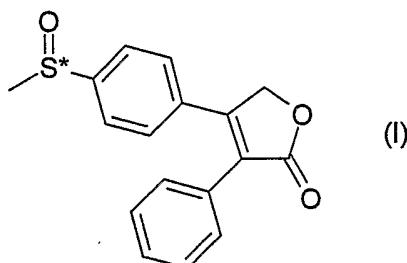
each of the two enantiomers thereof, and racemic and scalemic mixtures of the enantiomers.

2. A compound according to claim 1 which is one of:

10

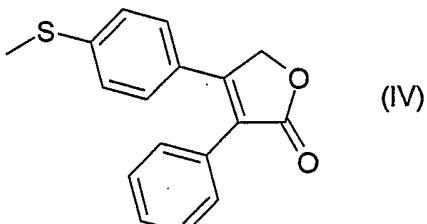
(R) 4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one  
(S) 4-[4(methylsulfinyl)phenyl]-3-phenylfuran-2(5H)-one

3. A process for the preparation of a compound of formula (I):



15

wherein a compound of formula (IV)



is reacted with with an oxidising agent.

4. A process according to claim 3 wherein the oxidising agent is either:

5 (a) sodium metaperiodate when racemic sulfinyl mixtures are to be obtained; or  
(b) a mixture of titanium tetrakisopropoxide, t-butyl hydroperoxide and either the (R,R) or the (S,S) forms of diethyl tartrate when it is desired to obtain an enantiomerically enriched compound of formula (I).

10 5. A process according to claim 4 wherein the reaction takes place in chlorinated solvents or a mixture of chlorinated solvents and C<sub>1</sub>-C<sub>4</sub> alcohols.

6. A process according to claim 5 wherein the chlorinated solvents are selected from 1,2-dichloroethane, methylene chloride, chloroform and mixtures thereof.

15

7. A compound of formula (I) as defined in claim 1 for use as a medicament.

8. A compound according to claim 7 for use in the treatment of a pathological condition or disease susceptible to amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2).

20 9. A pharmaceutical composition comprising a compound according to claim 1 or 2 in association with a pharmaceutically acceptable diluent or carrier.

25 10. Use of a compound according to claim 1 or 2, in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2).

30 11. Use according to claim 10, wherein the medicament is for use in the treatment of pain, fever or inflammation to inhibit prostanoid-induced smooth muscle contraction or for the prevention or treatment of colorectal cancer or neurodegenerative diseases.

35 12. Use of a compound according to claim 1 or 2 for the treatment of a pathological condition or disease susceptible to amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2).

13. Use according to claim 12, wherein the pathological condition or disease is pain, fever, inflammation, prostanoid-induced smooth muscle contraction, colorectal cancer or neurodegenerative diseases.

5

14. A method for treating a subject afflicted with a pathological condition or disease susceptible of amelioration by inhibition of the enzyme cyclooxygenase-2 (COX-2), which method comprises administering to the said subject an effective amount of a compound according to any of claims 1 or 2.

10

15. A method according to claim 14, wherein the pathological condition or disease is pain, fever or inflammation, prostanoid-induced smooth muscle contraction, colorectal cancer or neurodegenerative diseases.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/001296A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07D307/58 A61K31/341 A61P29/00

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 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, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PRASIT P ET AL: "The discovery of rofecoxib, 'MK 966, VioxxR), 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone!, an orally active cyclooxygenase-2 inhibitor" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 13, 5 July 1999 (1999-07-05), pages 1773-1778, XP004168837 ISSN: 0960-894X abstract; table 2 --- -/-	1-12

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## ° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search  13 May 2004	Date of mailing of the international search report  26/05/2004
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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP2004/001296

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PADAKANTI S ET AL: "A simple and rapid entry to 5-alkyl (aryl)-5-hydroxy-3,4-diaryl furan ones and 3a-hydroxy-1-aryl-2,3a,4,5-tetrahydronaphthofuranones via a tandem esterification and oxidative cyclization process" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 43, no. 48, 25 November 2002 (2002-11-25), pages 8715-8719, XP004390469 ISSN: 0040-4039 table 1	1-12
A	US 6 492 416 B1 (HA JUN-YONG ET AL) 10 December 2002 (2002-12-10) claim 1; examples 176,177,290-299,327,363-366,391-393	1-12
A	US 2002/013318 A1 (COGHLAN MICHAEL J ET AL) 31 January 2002 (2002-01-31) page 142, left-hand column; examples 15,33A,77,226H	1-12
A	HABEEB, AMGAD G. ET AL: "Design and syntheses of diarylisoxazoles: novel inhibitors of cyclooxygenase-2 ( COX - 2 ) with analgesic-antiinflammatory activity" DRUG DEVELOPMENT RESEARCH (2000), 51(4), 273-286 , XP008030648 page 283, left-hand column; table 1	1-12

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP2004/001296

### Box II Observations where certain claims were found unsearchable (Continuation of item 2 of 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.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  

Although claims 12-15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2.  Claims 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.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box 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 an additional fee, this Authority did not invite payment of any additional fee.
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 claims 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 claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP2004/001296

Patent document cited in search report		Publication date		Patent family member(s)	Publication date	
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