(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 592 680 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 1 (W1 B1)
Corrections, see
Description Paragraph(s) 5

(48) Corrigendum issued on:
25.03.2009 Bulletin 2009/13

(45) Date of publication and mention of the grant of the patent:
07.05.2008 Bulletin 2008/19

(21) Application number: **04710358.5**

(22) Date of filing: **12.02.2004**

(51) Int Cl.:
C07D 309/38 *(2006.01)* ***C07D 405/12*** *(2006.01)*
C07D 405/04 *(2006.01)* ***C07D 409/12*** *(2006.01)*
A61K 31/35 *(2006.01)* ***A61P 37/08*** *(2006.01)*

(86) International application number:
PCT/EP2004/001295

(87) International publication number:
WO 2004/072058 (26.08.2004 Gazette 2004/35)

(54) 2-PHENYLPYRAN-4-ONE DERIVATIVES AS SELECTIVE COX-2 INHIBITORS

2-PHENYLPYRAN-4-ON-DERIVATE ALS SELEKTIVE COX-2 INHIBITOREN

DERIVES DE 2-PHENYLPYRAN-4-ONE EN TANT QU'INHIBITEURS DE COX-2 SELECTIFS

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **13.02.2003 ES 200300355**

(43) Date of publication of application:
09.11.2005 Bulletin 2005/45

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WO-A-00/18753 **WO-A-01/68633**

EP 1 592 680 B9

Description

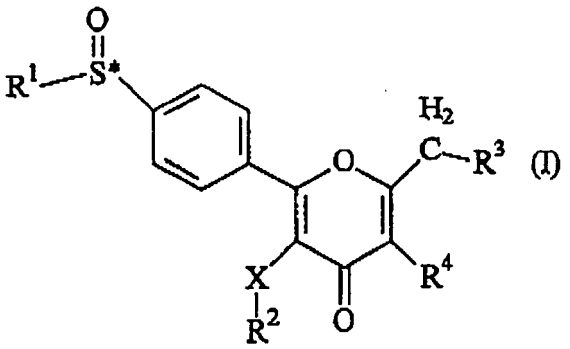
[0001] This invention relates to new therapeutically useful 2-phenylpyran-4-one derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use as medicaments.

[0002] It is known that non-selective inhibition of the enzyme cyclooxygenase (COX) prevents the overproduction of prostaglandins associated with inflammation, which is mediated by cyclooxygenase-2 (COX-2) but, at the same time, deprives tissues of basal 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.

[0003] WO 00/18753 discloses 2-phenylpyran-4-one derivatives with a sulfonyl group bound to the phenyl moiety as inhibitors of COX-2.

[0004] We have now found that certain 2-phenylpyran-4-one derivatives with a sulfinyl group bound to the phenyl moiety 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.

[0005] Accordingly the present invention provides a 2-phenylpyran-4-one compound of formula (I):



(I)

wherein:

R^1 represents an alkyl group;

R^2 represents an alkyl, C_3-C_7 cycloalkyl, pyridyl, thienyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono-ordialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^3 and R^4, which may be the same or different represent a hydrogen atom, or an alkyl,

alkenyl or alkynyl group which may be unsubstituted or substituted by one or more halogen atoms; and

X represents a single bond, an oxygen atom or a methylene group more preferably an oxygen atom;

said alkyl groups, said C_3-C_7 cycloalkyl group, said alkoxy group and the alkyl groups contained in said monoalkylamino and dialkylamino groups are each independently unsubstituted or substituted with 1, 2 or 3 substitutents which may be the same or different and are selected from halogen atoms, hydroxyl groups and alkoxy groups having from 1 to 4 carbon atoms, which alkoxy groups having from 1 to 4 carbon atoms are unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different and are selected from halogen atoms and hydroxyl groups; and

said hydroxyalkyl groups are hydroxyl(C_1-C_{10})alkyl groups and may be substituted with one or more hydroxyl radicals;

enantiomers thereof mixtures thereof and pharmaceutically acceptable salts thereof.

[0006] Typically, the alkyl groups are C_1-C_{20} alkyl groups, the alkoxy groups are C_1-C_{10} alkoxy groups, the mono- or dialkylamino groups are mono- or di(C_1-C_{10})alkylamino groups, the alkenyl groups are C_2-C_{20} alkenyl groups and the alkynyl groups are C_2-C_{20} alkynyl groups.

[0007] 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 the two different enantiomers if there are no other chiral centers in the compounds or in the form of various diastereomers should there be other chiral centers in the compounds. All these stereoisomeric compounds and their mixtures are encompassed in the present invention. The formulas used in the present description are intended to represent all possible stereoisomers or any mixture thereof. Compounds of formula (I) may have the (R) or (S) configuration at the sulphur atom of the sulfinyl group.

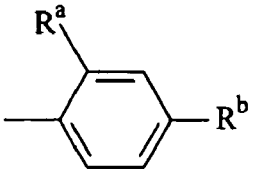
[0008] In a preferred embodiment the invention provides a compound of formula (I) wherein R^1 represents an unsubstituted alkyl group, more preferably a methyl group.

[0009] In another embodiment the present invention provides a compound of formula (I) wherein X represents a single bond or an oxygen atom, more preferably an oxygen atom.

[0010] In still another embodiment the present invention provides a compound of formula (I) wherein R^3 and R^4 represent a hydrogen atom or an unsubstituted C_{1-3} alkyl group, preferably a hydrogen atom.

[0011] In yet another embodiment the present invention provides a compound of formula (I) wherein R^2 represents a branched alkyl, C_3-C_7cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, an unsubstituted phenyl group or a phenyl group substituted by one or more halogen atoms, alkyl groups and/or alkoxy groups; more preferably an unsubstituted phenyl group or a phenyl group substituted by 1, 2 or 3 substituents independently selected from halogen atoms, methoxy group or methyl groups; still more preferably a phenyl group substituted by 1 or 2 substituents independently selected from halogen atoms and methyl groups.

[0012] Most preferably R^2 represents an optionally substituted phenyl group of formula:



wherein R^a and R^b are selected from the group consisting of hydrogen atoms, halogen atoms, alkyl groups and/or alkoxy groups, more preferably halogen atoms and still more preferably R^2 is a 2,4-difluorophenyl, 4-chloro-2-fluorophenyl or 4-bromo-2-fluorophenyl group.

[0013] Unless otherwise specified the term alkyl as used herein embraces optionally substituted, linear or branched radicals having 1 to 20 carbon atoms or, preferably 1 to 12 carbon atoms. More preferably alkyl radicals are "lower alkyl" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

[0014] Examples include methyl, ethyl, n-propyl, i-propyl, n-butyl, sec-butyl and tert-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, isopentyl, 1-ethylpropyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, n-hexyl or 1-ethylbutyl, 2-ethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dirnethylbutyl, 2,3-dimethylbutyl, 2-methylpentyl, 3-methylperityl; iso-hexyl radicals.

[0015] A said optionally substituted alkyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms. Typically, substituents on an alkyl group are themselves unsubstituted.

[0016] When it is mentioned that alkyl radicals may be optionally substituted it is meant to include linear or branched alkyl radicals as defined above, which may be unsubstituted or substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, said substituents may be the same or different.

[0017] As used herein, the term alkenyl embraces linear or branched, mono or polyunsaturated radicals having 2 to 20 carbon atoms or, preferably, 2 to 12 carbon atoms. More preferably alkenyl radicals are "lower alkenyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular it is preferred that the alkenyl radicals are mono or diunsaturated.

[0018] Examples include vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl; 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl and 4-pentenyl radicals.

[0019] When it is mentioned that alkenyl radicals may be optionally substituted it is meant to include linear or branched alkenyl radicals as defined above, which may be unsubstituted or substituted in any position by one or more specified substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, said substituents may be the same or different.

[0020] A said optionally substituted alkenyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are selected from halogen atoms, preferably fluorine atoms.

[0021] As used herein, the term alkynyl embraces linear or branched, mono or polyunsaturated radicals having 2 to 20 carbon atoms or, preferably, 2 to 12 carbon atoms. More preferably, alkynyl radicals are "lower alkynyl" radicals having 2 to 8, preferably 2 to 6 and more preferably 2 to 4 carbon atoms. In particular, it is preferred that the alkynyl radicals are mono or diunsaturated.

[0022] Examples include 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl and 3-butynyl radicals.

[0023] When it is mentioned that alkynyl radicals may be optionally substituted it is meant to include linear or branched alkynyl radicals as defined above, which may be unsubstituted or substituted in any position by one or more specified substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, said substituents may be the same or different.

[0024] A said optionally substituted alkynyl group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are selected from halogen atoms, preferably fluorine atoms.

[0025] As used herein, the term alkoxy (or alkyloxy) embraces optionally substituted, linear or branched oxy-containing radicals each having alkyl portions of 1 to 10 carbon atoms. More preferred alkoxy radicals are "lower alkoxy" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

[0026] An alkoxy group is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms.

[0027] Preferred alkoxy radicals include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy or 2-hydroxypropoxy.

[0028] As used herein, the term monoalkylamino embraces radicals containing an optionally substituted, linear or branched alkyl radical of 1 to 10 carbon atoms attached to a divalent-NH- radical. More preferred monoalkylamino radicals are "lower monoalkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms.

[0029] A monoalkylamino group typically contains an alkyl group which is unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms.

[0030] Preferred optionally substituted monoalkylamino radicals include methylamino, ethylamino, n-propylamino, i-propylamino, n-butylamino, sec-butylamino, t-butylamino, trifluoromethylamino, difluoromethylamino, hydroxymethylamino, 2-hydroxyethylamino or 2-hydroxypropylamino.

[0031] As used herein, the term dialkylamino embraces radicals containing a trivalent nitrogen atom with two optionally substituted, linear or branched alkyl radicals of 1 to 10 carbon atoms attached thereto. More preferred dialkylamino radicals are "lower dialkylamino" radicals having 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms in each alkyl radical.

[0032] A dialkylamino group typically contains two alkyl groups, each of which is unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms.

[0033] Preferred optionally substituted dialkylamino radicals include dimethylamino, diethylamino, methyl(ethyl)amino, di(n-propyl)amino, n-propyl(methyl)amino, n-propyl(ethyl)amino, di(i-propyl)amino, i-propyl(methyl)amino, i-propyl(ethyl)amino, di(n-butyl)amino, n-butyl(methyl)amino, n-butyl(ethyl)amino, n-butyl(i-propyl)amino, di(sec-butyl)amino, sec-butyl(methyl)amino, sec-butyl(ethyl)amino, sec-butyl(n-propyl)amino, sec-butyl(i-propyl)amino, di(t-butyl)amino, t-butyl(methyl)amino, t-butyl(ethyl)amino, t-butyl(n-propyl)amino, t-butyl(i-propyl)amino, trifluoromethyl(methyl)amino, trifluoromethyl(ethyl)amino, trifluoromethyl(n-propyl)amino, trifluoromethyl(i-propyl)amino, trifluoromethyl(n-butyl)amino, trifluoromethyl(sec-butyl)amino, difluoromethyl(methyl)amino, difluoromethyl(ethyl)amino, difluoromethyl(n-propyl)amino, difluoromethyl(i-propyl)amino, difluoromethyl(n-butyl))amino, difluoromethyl(sec-butyl)amino, difluoromethyl(t-butyl)amino, difluoromethyl(trifluoromethyl)amino, hydroxymethyl(methyl)amino, ethyl(hydroxymethyl)amino, hydroxymethyl(n-propyl)amino, hydroxymethyl(i-propyl)amino, n-butyl(hydroxymethyl)amino, sec-butyl(hydroxymethyl)amino, t-butyl(hydroxymethyl)amino, difluoromethyl(hydroxymethyl)amino, hydroxymethyl(trifluoromethyl)amino, hydroxyethyl(methyl)amino, ethyl(hydroxyethyl)amino, hydroxyethyl(n-propyl)amino, hydroxyethyl(i-propyl)amino, n-butyl(hydroxyethyl)amino, sec-butyl(hydroxyethyl)amino, t-butyl(hydroxyethyl)amino, difluoromethyl(hydroxyethyl)amino, hydroxyethyl(trifluoromethyl)amino, hydroxypropyl(methyl)amino, ethyl(hydroxypropyl)amino, hydroxypropyl(n-propyl)amino, hydroxypropyl(i-propyl)amino, n-butyl(hydroxypropyl)amino, sec-butyl(hydroxypropyl)amino, t-butyl(hydroxypropyl)amino, difluoromethyl(hydroxypropyl)amino, hydroxypropyl(trifluoromethyl)amino.

[0034] As used herein, the term hydroxyalkyl embraces linear or branched alkyl radicals having 1 to 10 carbon atoms, preferably 1 to 6 carbon atoms, any one of which may be substituted with one or more hydroxyl radicals.

[0035] Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.

[0036] As used herein, the term cycloalkyl embraces saturated carbocyclic radicals and, unless otherwise specified, a cycloalkyl radical typically has from 3 to 7 carbon atoms.

[0037] A cycloalkyl radical is typically unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different. The substituents are preferably selected from halogen atoms, preferably fluorine atoms, hydroxy groups

and alkoxy groups having from 1 to 4 carbon atoms. When a cycloalkyl radical carries 2 or more substituents, the substituents maybe the same or different.

[0038] Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. It is preferably cyclopropyl, cyclopentyl or cyclohexyl. When a cycloalkyl radical carries 2 or more substituents, the substituents may be the same or different.

[0039] As used herein, the term halogen atom embraces chlorine, fluorine, bromine or iodine atom typically a fluorine, chlorine or bromine atom, most preferably chlorine or fluorine. The term halo when used as a prefix has the same meaning.

[0040] As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkaline earth metal (e.g. calcium cr magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

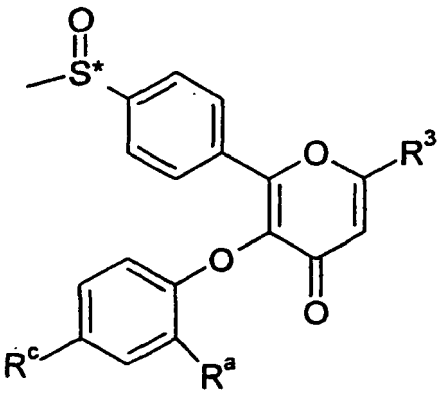
[0041] In a phenyl group substituted by one or more halogen atoms or alkyl, trifluoroalkyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkyl amino, hydroxyalkyl or hydroxycarbonyl groups, the phenyl ring may be substituted by 1, 2, 3, 4 or 5 substituents, preferably 1, 2 or 3 substituents, each being independently selected from the possible substituents set out above. That is to say, the phenyl group (attached to X or the pyran-4-one ring through its 1-position) may be substituted at any of the remaining positions, that is to say the 2, 3, 4, 5 or 6-positions. A phenyl group having more than one substituent may be substituted at any combination of positions. For example a phenyl group having two substituents may be substituted at the 2 and 3, 2 and 4, 2 and 5, 2 and 6, 3 and 4 or3 and 5 positions.

[0042] Specific examples of the 2-phanylpyran-4-one derivatives of the present invention include:

3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(2,4-difluorophenoxy)-6-ethyl-5-methyl-2-[(4-(methylsulfinylphenyl)]-4H-pyran-4-one;
3-(4-fluoro-2-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(4-chloro-2-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2-chloro-4-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2-bromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(3-bromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(4-bromo-2-chlocophenoxy)-6-methyt-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2,4-dibromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2,4-difluorophenoxy)-6-methyl-2-[(4-(ethylsulfinyl)phenyl]-4H-pyran-4-one;
6-methyl-3-(2-methylphenoxy)-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
6-methyl-3-(3-methylphenoxy)2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2-fluoro-4-methylphenoxy)- 6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;

[0043] in the form of all possible enantiomers and mixtures thereof and pharmaceutically acceptable salts thereof.

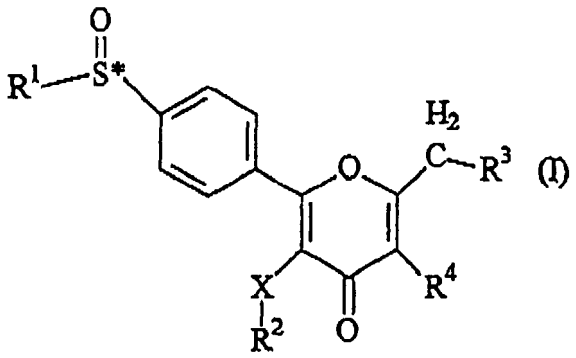
[0044] Of outstanding interest are compounds of formula:



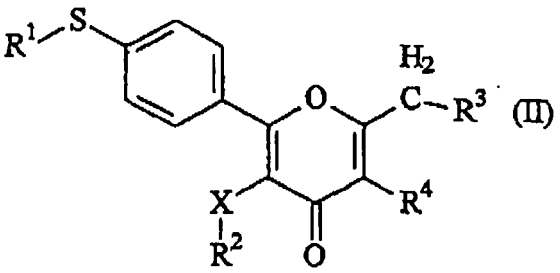
Example	R^3	R^a	R^c	Configuration
1	Me	F	F	Racemic
2	Me	F	F	Enantiomer 1a
3	Me	F	F	Enantiomer 1b
4	Me	F	Cl	Racemic
5	Me	F	Cl	Enantiomer 4a
6	Me	F	Cl	Enantiomer 4b
7	Me	F	Br	Racemic
8	Me	F	Br	Enantiomer 7a
9	Me	F	Br	Enantiomer 7b

in the form of all possible enantiomers and mixtures thereof and pharmaceutically acceptable salts thereof.

[0045] The present invention also provides processes for preparing a compound of formula (I)



wherein R^1, R^2, R^3, R^4 and X are as defined above by reacting a mercapto derivative of formula (II):



wherein R^1, R^2, R^3, R^4 and X are as defined above with an oxidizing agent, preferably sodium metaperiodate when it is desired to obtain racemic mixtures of compounds or using a mixture of titanium tetraisopropoxide, 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, namely (R) or (S) configuration.

[0046] The reaction between the mercapto derivative of formula (II) and the oxidizing agent is preferably carried out in an organic solvent, preferably a chlorinated solvent or a mixture of chlorinated solvents and C_1-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 C_1-C_4 alcohol is preferably selected from methanol and ethanol. Preferred solvent systems are 1,2-dichloroethane or a mixture of methylene chloride with methanol or ethanol.

[0047] The mercapto derivatives of formula (II) are known and can be prepared following the teachings of WO 01/68633

A1.

[0048] The 2-phenylpyran-4-one derivatives of formula (I) in which a basic group is present can be converted by methods known per se into pharmaceutically acceptable salts, preferably acid addition salts by treatment with organic or inorganic acids such as fumaric, tartaric, succinic or hydrochloric acid.

[0049] The following biological tests and data further illustrate this invention.

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

[0050] 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 activity determination, 500 μl aliquots of blood were incubated with either 5 μl vehicle (dimethylsulphoxide) or 5 μl of a test compound for 24 h at 37°C. Calcium ionophore A23187 (25 μM) was added 20 min before stopping the incubation. Plasma was separated by centrifugation (10 min at 13000 rpm) and kept at -30°C until TXB_2 levels were measured using an enzyme immunoassay kit (EIA).

[0051] The effect of the compounds was evaluated by incubating each compound at five to six different concentrations with triplicate determinations. IC_{50} values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer.

[0052] 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_2 levels were measured using an enzyme immunoassay kit (EIA). The effects of inhibitors were studied by incubating each compound (5 μl aliquots) at five to six different concentrations with duplicate determinations in the presence of LPS for 24 hours. IC_{50} values were obtained by non-linear regression using InPlot, GraphPad software on an IBM computer.

[0053] The results obtained from the biological assays are shown in Table 1.

TABLE 1: COX and COX-2 Inhibition

Example	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	Ratio COX-1/COX 2
1	100	0.96	104
2	100	2,1	48
3	86.6	0.27	321
4	81,1.3	0.37	219
5	72,9	2,47	30
6	100	0,25	400
7	77.0	0 57	135
8	32,1	1, 58	20
9	73,1	0,17	430

[0054] As shown in Table 1, the 2-phanylpyran-4-one derivatives of formula (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.

[0055] 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. Some of the compounds of the present invention have also shown an unexpected pharmacokinetic profile.

[0056] Preferred compounds of the invention have an IC_{50} value for COX-2 of less than 50 μM, preferably less than 10μM more preferably less than 5μM, still more preferably less than 2,5μM. Preferred compounds of the invention also have an IC_{50} value for COX-1 of greater than 10μM preferably greater than 20μM. As an indicator of selectivity for inhibition of COX-2 over COX 1, the ratio of COX-1/COX-2 IC_{50} values is preferably greaterthan 10, more preferably greater than 20, still more preferably greater than 50.

[0057] The present invention further provides a compound of formula (I) for use in a 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.

[0058] 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 or neurodegenerative diseases for example, Alzheimer's disease.

[0059] 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, osteoarthritis, gouty arthritis, spondyloarthopathies, 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 ortreatment of colorectal cancer or neurodegenerative diseases, for example, Alzheimers disease.

[0060] 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.

[0061] 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, gastrointestinal bleeding and coagulation disorders, kidney disease (e.g. impaired renal function), those prior to surgery or taking anticoagulants, and those susceptible to non-steroidal anti-inflammatory drugs induced asthma.

[0062] The compounds can further be used to treat inflammation in diseases such as 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.

[0063] Compounds of the present invention are inhibitors of cyclooxygenase-2 enzyme and are thereby useful to treat the cyclooxygenase-2 mediated diseases enumerated above.

[0064] Accordingly, the compounds of the present invention and pharmaceutically acceptable salts thereof, and pharmaceutical compositions comprising such compounds and/or salts thereof, 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 a compound or a pharmaceutically acceptable salt thereof.

[0065] The present invention also provides pharmaceutical compositions, which comprise, as an active ingredient, at least a 2-phenylpyran-4-one derivative of formula (I) or a pharmacologically acceptable salt thereof 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.

[0066] Preferably the compositions are made up in a form suitable for oral, topical, nasal, inhalation, rectal, percutaneous or injectable administration.

[0067] The pharmaceutically acceptable excipients that are admixed with the active compound or salts of such compound, to form the compositions of this invention are known per se and the actual excipients used depend inter alia on the intended method of administering the compositions.

[0068] 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.

[0069] 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 and 500 mg of active ingredient or the equivalent amount of a salt thereof.

[0070] The liquid composition adapted for oral use may be in the form of solutions or suspensions. The solutions may be aqueous solutions of a soluble salt or other derivative 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 or a pharmaceutically acceptable salt thereof in association with water, together with a suspending agent or flavouring agent.

[0071] Compositions for parenteral injection may be prepared from soluble salts, which may or may not be freeze-dried and which may be dissolved in pyrogen free aqueous media or other appropriate parenteral injection fluid.

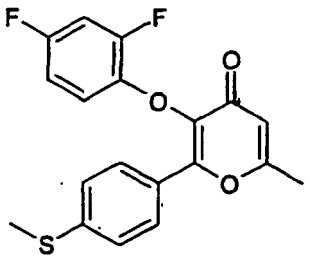
[0072] Effective doses are normally in the range of 10-600 mg of active ingredient per day. Daily dosage may be administered in one or more treatments, preferably from 1 to 4 treatments, per day.

[0073] The invention is illustrated by the following Preparations and Examples, which do not limit the scope of the invention in any way.

PREPARATION 1

3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylthio)phenyl]-4*H*-pyran-4-one

[0074]



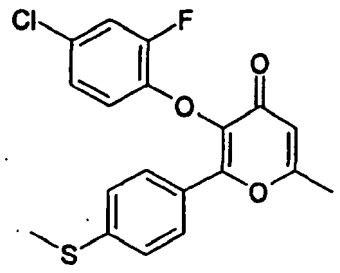
a) To a solution of 2,4-difluorophenol (1.04 g; 8 mmol) and 2-bromo-1-[4-(methylthio)phenyl]ethanone (1.96 g, 8 mmol) in methylene chloride (13 ml) was added a solution of potassium carbonate (1.66 g) and tetrabutylammonium hydrogensulfate (0.14 g) in water (5 ml). The mixture was stirred at room temperature for 16 hours. Water (100 ml) was added, the organic phase was decanted, and the basic phase was extracted with methylene chloride (2 x 100 ml). The organic solution was dried (Na_2SO_4) and the solvent removed under reduced pressure. The resulting solid was washed with ethyl ether. 2-(2,4-Difluorophenoxy)-1-[4-(methyfthio)phenyl]ethanone was obtained (1.69 g, 72%) as an off-white solid.

b) The above compound (1.68 g, 5.7 mmol) was added to a solution of polyphosphoric acid. (19 g) in acetic anhydride (8.5 ml), pre-heated at 95-100°C. The mixture was heated at the same temperature for 5 hours. After cooling, the reaction was poured into ice-water, extracted with ethyl acetate (3 x 100 ml), the organic solution was washed with saturated sodium bicarbonate (2x100 ml), water and brine, dried (Na_2SO_4), and the solvent removed under reduced pressure. The residual oil was purified by column chromatography with silica gel and ethyl acetate/n-hexane (1/1) as eluent. 3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylthio)phenyl]-4H-pyran-4-one (0.37 g, 17%) was obtained as an off-white solid.
δ (DMSO): 2.41 (s, 3H), 2.50 (s, 3H), 6.40 (s, 1 H), 6.94 (m, 2H), 7.39 (m, 3H), 7.76 (d, J=8.4 Hz, 2H).

PREPARATION 2

3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylthio)phenyl]-4*H*-pyran-4-one

[0075]

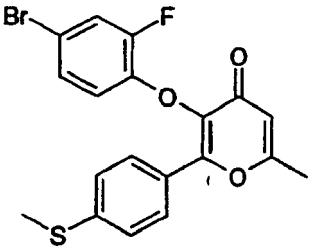


[0076] Obtained as an off white solid (16% overall) from 2-bromo-1-[4-(methylthio)phenyl]-ethanone and 4-chloro-2-fluorophenol by the procedure described in Preparation 1.
δ (DMSO): 2.42 (s, 3H), 2.50 (s, 3H), 6.30 (s, 1H), 6.73 (dd, J_{HH}=J_{HF}=9.0 Hz, 1 H), 6.94 (m, 1H), 7.14 (dd, J=10.5, 2.4 Hz, 1H), 7.27 (d, J=8.7 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H).

PREPARATION 3

3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylthio)phenyl]-4*H*-pyran-4-one

[0077]

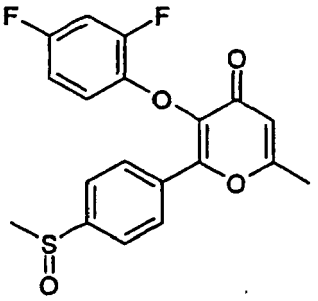


[0078] Obtained as an off-white solid (17% overall) from 2-bromo-1-[4-(methylthio)phenyl]-ethanone and 4-bromo-2-fluorophenol by the procedure described in Preparation 1:
δ (DMSO): 2.42 (s, 3H), 2.50 (s, 3H), 6.31 (s, 1H), 6.68 (dd, J_{HH}=J_{HF}=8.7 Hz, 1 H), 7.07 (m, 1 H), 7.26-7.30 (m, 3H), 7.82 (d, J=8.7 Hz, 2H).

EXAMPLE 1

3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one

[0079]



[0080] To a solution of the title compound of Preparation 1 (1.36 g, 3.8 mmol) in methanol (17 ml) was added dropwise a solution of sodium metaperiodate (0.80 g) in water (10 ml) at 0°C and this mixture was stirred at this temperature for 2 h and 3 d at r.t. Then, the reaction was poured into water, extracted with ethyl acetate (3 x 100 ml), the organic solution dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was purified by column chromatography with silica gel and dichloromethane/ethyl acetate/methanovacetic acid (78/17/3/2) as eluent. 3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H pyran-4-one (1.09 g, 77%) was obtained as an off-white solid.
m.p.: 158-159°C
δ (DMSO): 2.44 (s, 3H), 2.76 (s, 3H), 6.32 (s, 1H), 6.67-6.92 (m, 3H), 7.74 (d, J=6.8 Hz, 2H), 8.08 (d, J=6.8 Hz, 2H).

EXAMPLE 2

3-(2,4-Difluorophenoxy)-6-methyl-2-[4(methylsulfinyl)phenyl]-4H-pyran-4-one-Enantiomer 1a

[0081] 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 (1.26 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_2SO_4)

and the solvent removed under reduced pressure. The residue was purified by flash chromatography and ethyl acetate/ methanol (95/5) as eluent. 3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one (0.18 g, 17%, 100% ee) was obtained as an off-white solid.
$[\alpha]_D^{22}$ = +82.3 (c 0.25, MeOH)
m.p.: 158-159°C
δ (DMSO): 2.44 (s, 3H), 2.76 (s, 3H), 6.32 (s, 1H), 6.67-6.92 (m, 3H), 7.74 (d, J=6.8 Hz. 2H), 8.08 (d, J=6.8 Hz, 2H).

EXAMPLE 3

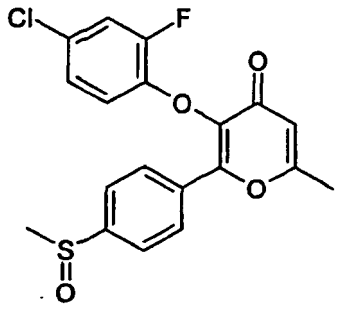
3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one - Enantiomer 1b

[0082] Obtained as an off-white solid (57%, 88.4% ee) from the title compound of Preparation 1 and (S,S)-diethyl tartrate by the procedure described in Example 2.
$[\alpha]_D$22 = -71.5 (c 0-25, MeOH)
m.p.: 158-159°C
δ (DMSO): 2.4.4 (s, 3H), 2.76 (s, 3H), 6.32 (s, 1H), 6.67-6.92 (in, 3H), 7.74 (d, J=6.8 Hz, 2H), 8.08 (d, J=6.8 Hz, 2H)..

EXAMPLE 4

3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one

[0083]



[0084] Obtained as an off-white solid (55%) from the title compound of Preparation 2 and sodium metaperiodate by the procedure described in Example 1.
m.p.: 186-188°C
δ (DMSO): 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.03-7.15 (m, 2H), 7.56 (dd, J=10.8, 2.4 Hz, 1H), 7.84 (d, J=8.6 Hz, 2H), 7.99 (d, J=8.6 Hz, 2H).

EXAMPLE 5

3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one-Enantiomer 4a

[0085] Obtained as an off-white solid (48%, 100% ee) from the title compound of Preparation 2 and (R,R)-diethyl tartrate by the procedure described in Example 2.
$[\alpha]_D^{22}$= +77.7 (c 0.25, MeOH)
m.p.: 186-188°C
δ (DMSO): 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.03-7.15 (m, 2H), 7.56 (dd, J=10.8, 2.4 Hz, 1H), 7.84 (d, J=8.6 Hz, 2H), 7.99 (d, J=8.6 Hz, 2H).

EXAMPLE 6

3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one-Enantiomer 4b

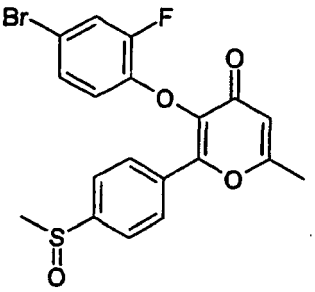
[0086] Obtained as an off-white solid (49%, 98.4% ee) from the title compound of Preparation 2 and (S,S)-diethyl

tartrate by the procedure described in Example 2.
$[\alpha]_D^{22}$ = -77.0 (c 0.25, MeOH)
m.p.: 186-188°C
δ (DMSO): 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.03-7.15 (m, 2H), 7.56 (dd, J=10.8, 2.4 Hz, 1H), 7.84 (d, J=8.6 Hz, 2H), 7.99 (d, J=8.6 Hz, 2H).

EXAMPLE 7

3-(4-Bromo-2-nuorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one

[0087]



[0088] Obtained as an off-white solid (43%) from the title compound of Preparation 3 and sodium metaperiodate by the procedure described in Example 1.
m.p.: 201 °C
δ (DMSO):. 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.01 (dd, J_{HH}=J_{HF}=9-0 Hz, 1H), 7.24 (m, 1H), 7.66 (dd, J=10.8, 2.1 Hz, 1H), 7.84 (d, J=8.7 Hz, 2H), 7.98 (d, J=8.7 Hz, 2H).

EXAMPLE 8

3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one-Enantiomer 7a

[0089] Obtained as an off-white solid (48%, 98.8% ee) from the title compound of Preparation, 3 and (R,R)-diethyl tartrate by the procedure described in Example 2.
$[\alpha]_D^{22}$ = +68.0 (c 0.5, MeOH)
m.p.: 201°C
δ (DMSO): 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.01 (dd, J_{HH}=J_{HF}=9.0 Hz, 1 H), 7.24 (m, 1H), 7.66 (dd, J=10.8, 2.1 Hz, 1H), 7.84 (d, J=8.7 Hz, 2H), 7.98 (d, J=8.7 Hz, 2H).

EXAMPLE 9

3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one-Enantiomer 7b

[0090] Obtained as an off-white solid (53%, 98.2% ee) from the title compound of Preparation 3 and (S,S)-diethyl tartrate by the procedure described in Example 2.
$[\alpha]_D^{22}$= -71.3 (c 0.5, MeOH)
m.p.: 201°C
δ (DMSO): 2.43 (s, 3H), 2.78 (s, 3H), 6.47 (s, 1H), 7.01 (dd, J_{HH}=J_{HF}=9.0 Hz, 1H), 7.24 (m, 1 H), 7.66 (dd, J=10.8, 2.1 Hz, 1H), 7.84 (d, J=8.7 Hz, 2H), 7.98 (d, J=8.7 Hz, 2H).

EXAMPLE 10

Capsules

[0091] 25,000 capsules each containing 100 mg of 3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one (active ingredient) were prepared according to the following formulation:

Active ingredient	2.5	Kg
Lactose monohydrate	5	Kg
Colloidal silicon dioxide	0.05	Kg
Com starch	0.5	Kg
Magnesium stearate	0.1	Kg

Procedure

[0092] The above ingredients were sieved through a 60 mesh sieve, and were loaded into a suitable mixer and filled into 25,000 gelatine capsules.

EXAMPLE 11

Tablets

[0093] 100,000 Tablets each containing 50 mg of 3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one (active ingredient) were prepared from the following formulation:

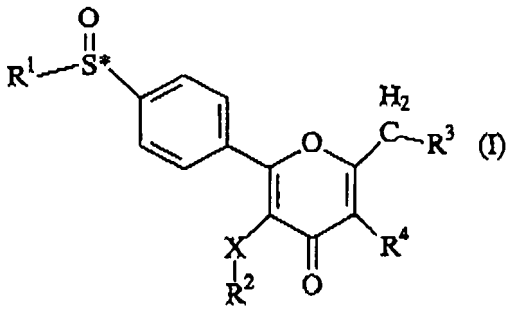
Active ingredient	5	Kg
Spray dried lactose	1 9.9	Kg
Microcrystalline cellulose	3.9	Kg
Sodium stearyl fumarate	0.2	Kg
Colloidal silicon dioxide	0.2	Kg
Carboxymethyl starch	0.8	Kg

Procedure

[0094] All the powders were passed through a screen with an aperture of 0.6 mm, then mixed in a suitable mixer for 20 minutes, and compressed into 300 mg tablets using 9 mm disc and flat bevelled punches. The disintegration time of the tablets was about 3 minutes.

Claims

1. A compound of formula (I):



wherein

- R^1 represents an alkyl group;
- R^2 represents an alkyl, C_3-C_7 cycloalkyl, pyridyl, thienyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;
- R^3 and R^4, which may be the same or different represent a hydrogen atom, or an alkyl, alkenyl or alkynyl

group which may be unsubstituted or substituted by one or more halogen atoms;
• X represents a single bond, an oxygen atom, or a methylene group;
• said alkyl groups, said C_3-C_7 cycloalkyl group, said alkoxy group and the alkyl groups contained in said monoalkylamino and dialkylamino groups are each independently unsubstituted or substituted with 1, 2 or 3 substitutents which may be the same or different and are selected from halogen atoms, hydroxy groups and alkoxy groups having from 1 to 4 carbon atoms, which alkoxy groups having from 1 to 4 carbon atoms are unsubstituted or substituted with 1, 2 or 3 substituents which may be the same or different and are selected from halogen atoms and hydroxy groups; and
• said hydroxyalkyl groups are hydroxy(C_1-C_{10})alkyl groups and may be substituted with one or more hydroxyl radicals;

enantiomers thereof mixtures thereof and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein the alkyl groups are C_1-C_{20} alkyl groups, the alkoxy groups are C_1-C_{10} alkoxy groups, the mono- or dialkylamino groups are mono- or di(C_1-C_{10})alkylamino groups, the alkenyl groups are C_2-C_{20} alkenyl groups and the alkynyl groups are C_2-C_{20} alkynyl groups.

3. A compound according to claim 1 or claim 2 wherein R^1 represents an unsubstituted alkyl group.

4. A compound according to claim 3 wherein R^1 is a methyl group.

5. A compound according to any one of claims 1 to 4 wherein X represents an oxygen atom

6. A compound according to any one of claims 1 to 5 wherein R^3 and R^4 represent a hydrogen atom or an unsubstituted C_{1-3} alkyl group.

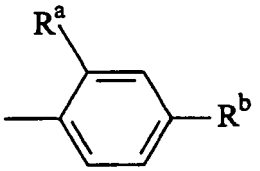
7. A compound according to claim 6 wherein R^3 and R^4 represents a hydrogen atom.

8. A compound according to any one of claims 1 to 7 wherein R^2 is a branched alkyl, C_3-C_7 cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, an unsubstituted phenyl group or a phenyl group substituted by one or more halogen atoms, alkyl groups and/or alkoxy groups.

9. A compound according to claim 8 wherein R^2 is an unsubstituted phenyl group or a phenyl group substituted by 1, 2 or 3 substituents independently selected from halogen atoms, methoxy group or methyl groups.

10. A compound according to claim 9 wherein R^2 represents a phenyl group substituted by 1 or 2 substituents independently selected from halogen atoms and methyl groups.

11. A compound according to claim 8 wherein R^2 represents an optionally substituted phenyl group of formula



wherein R^a and R^b are selected from the group consisting of hydrogen atoms, halogen atoms, alkyl groups and/or alkoxy groups.

12. A compound according to claim 11 wherein R^a and R^b are selected from halogen atoms

13. A compound according to claim 12 wherein R^2 is a 2,4-difluorophenyl, 4-chloro-2-fluorophenyl or 4-bromo-2-fluorophenyl group.

14. A compound according to any one of claims 1 to 3 and 5 to 10 which is:

3-(2.4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran-4-one
3-(2,4-difluorophenoxy)-6-ethyl-5-methyl-2-[(4-(methylsulfinylphenyl)]-4H-pyran-4-one;
3-(4-fluoro-2-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(4-chloro-2-methylphanoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2-chloro-4-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2-bromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(3-bromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(4-bromo-2-chlorophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2,4-dibromophenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
3-(2,4-difluorophenoxy)-6-methy)-2-[(4-(ethytsu)finyl)phenyl]-4H-pyran-4-one;
6-methyl-3-(2-methylphenoxy)-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;
6-methyl-3-(3-methylphenoxy)-2-[(4-(methylsulflnyl)phenyl]-4H-pyran-4-one;
3-(2-fluoro-4-methylphenoxy)- 6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-one;

enantiomers thereof, mixtures thereof and pharmaceutically acceptable salts thereof.

15. A compound according to any one of claims 1 to 14 in which the sulphur atom of the sulfinyl group has the (S) configuration.

16. A compound according to any one of claims 1 to 14 in which the sulphur atom of the sulfinyl group has the (R) configuration.

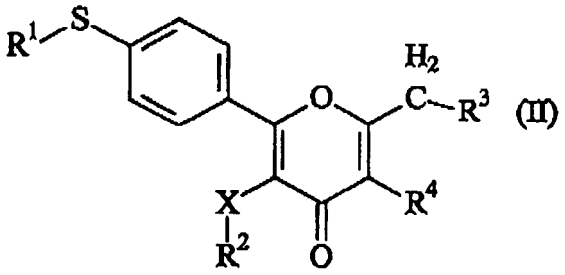
17. A compound according to any one of claims 1 to 3 and 5 to 10 which is:

3-(2,4-Difluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-one
3-(4-Chloro-2-fluorophenoxy)-6-methyl-2-[4-(methylsulflnyl)phenyl]-4*H*-pyran-4-one
3-(4-Bromo-2-fluorophenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4*H*-pyran4- one

in the form of the (-) configuration enantiomers, mixtures thereof and pharmaceutically acceptable salts thereof.

18. A process for producing a compound of formula (I) as defined in any one of claims 1 to 16 which process comprises:

(a) reacting a mercapto derivative of formula (II):



wherein R^1, R^2, R^3, R^4 and X are as defined in claim 1. with an oxidising agent.

19. A process according to claim 18 wherein the oxidising agent is either

(a) sodium metaperiodate when racemic sulfinyl mixtures are to be obtained; or
(b) a mixture of titanium tetraisopropoxide, 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).

20. A process according to claim 19 wherein the reaction takes place in chlorinated solvents or a mixture of chlorinated solvents and C_1-C_4 alcohols.

21. A process according to claim 20 wherein the chlorinated solvent is selected from 1,2-dichloroethane, methylene chloride, chloroform and mixtures thereof.

22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 17 or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

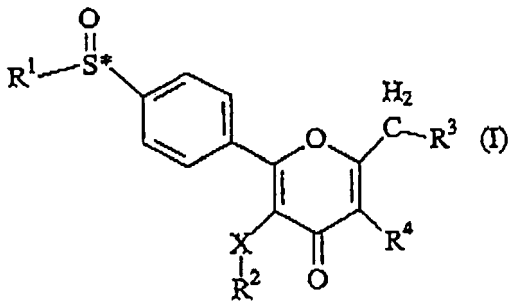
23. A compound according to any one of claims 1 to 17 or a composition according to claim 22 for use in a method of treatment of the human or animal body by therapy.

24. Use of a compound according to any one of claims 1 to 17 or pharmaceutically acceptable salt thereof or a composition according to claim 22 for the manufacture of a medicament 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.

25. A compound according to any one of claims 1 to 17 or a composition according to claim 22 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.

Patentansprüche

1. Verbindung der Formel (I):



(I)

worin

- R^1 eine Alkylgruppe verkörpert;
- R^2 eine Alkyl-, C_3-C_7-Cycloalkyl-, Pyridyl-, Thienyl-, Naphthyl-, Tetrahydronaphthyl- oder Indanylgruppe oder eine Phenylgruppe, die unsubstituiert oder durch ein oder mehrere Halogenatome oder Alkyl-, Trifluormethyl-, Hydroxy-, Alkoxy-, Methylthio-, Amino-, Mono- oder Dialkylamino-, Hydroxyalkyl- oder Hydroxycarbonylgruppen substituiert sein kann, verkörpert;
- R^3 und R^9, die gleich oder verschieden sein können, ein Wasserstoffatom oder eine Alkyl-, Alkenyl- oder Alkinylgruppe verkörpern, die unsubstituiert oder substituiert sein kann durch ein oder mehrere Halogenatome;
- X eine Einfachbindung, ein Sauerstoffatom oder eine Methylengruppe verkörpert;
- die genannten Alkylgruppen, die genannte C_3-C_7-Cycloalkylgruppe, die genannte Alkoxygruppe und die in den genannten Monoalkylamino- und Dialkylaminogruppen enthaltenen Alkylgruppen sind jeweils unabhängig unsubstituiert oder substituiert mit 1, 2 oder 3 Substituenten, die gleich oder unterschiedlich sein können und ausgewählt sind aus Halogenatomen, Hydroxygruppen und Alkoxygruppen mit 1 bis 4 Kohlenstoffatomen, wobei die Alkoxygruppen 1 bis 4 Kohlenstoffatome besitzen, die unsubstituiert oder substituiert sind mit 1, 2 oder 3 Substituenten, die gleich sein können oder unterschiedlich und die ausgewählt sind aus Halogenatomen und Hydroxygruppen; und
- die genannten Hydroxyalkylgruppen sind Hydroxy(C_1-C_{10})alkylgruppen und können mit einem oder mehreren Hydroxylresten substituiert sein;

Enantiomere davon, Mischungen davon und pharmazeutisch verträgliche Salze davon.

2. Verbindung gemäß Anspruch 1, wobei die Alkylgruppen C_1-C_{20}-Alkylgruppen sind, die Alkoxygruppen C_1-C_{10}-Alkoxygruppen sind, die Mono- oder Dialkylaminogruppen Mono- oder Di(C_1-C_{10}) alkylaminogruppen sind, die Alkenylgruppen C_2-C_{20}-Alkenylgruppen sind und die Alkinylgruppen C_2-C_{20}-Alkinylgruppen sind.

3. Verbindung gemäß Anspruch 1 oder Anspruch 2, wobei R^1 eine unsubstituierte Alkylgruppe verkörpert.

4. Verbindung gemäß Anspruch 3, wobei R^1 eine Methylgruppe ist.

5. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 4, wobei X ein Sauerstoffatom verkörpert.

6. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 5, wobei R^3 und R^4 ein Wasserstoffatom oder eine unsubstituierte C_{1-3}-Alkylgruppe verkörpern.

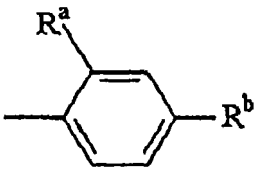
7. Verbindung gemäß Anspruch 6, wobei R^3 und R^4 ein Wasserstoffatom verkörpern.

8. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 7, wobei R^2 eine verzweigte Alkyl-, C_3-C_7-Cycloalkyl-, Naphthyl-, Tetrahydronaphthyl- oder Indanylgruppe, eine unsubstituierte Phenylgruppe oder eine Phenylgruppe, die durch ein oder mehrere Halogenatome, Alkylgruppen und/oder Alkoxygruppen substituiert ist, ist.

9. Verbindung gemäß Anspruch 8, wobei R^2 eine unsubstituierte Phenylgruppe ist oder eine Phenylgruppe, substituiert durch 1, 2 oder 3 Substituenten, unabhängig ausgewählt aus Halogenatomen, einer Methoxygruppe oder Methylgruppen.

10. Verbindung gemäß Anspruch 9, wobei R^2 eine Phenylgruppe, substituiert durch 1 oder 2 Substituenten, unabhängig ausgewählt aus Halogenatomen und Methylgruppen, ist.

11. Verbindung gemäß Anspruch 8, wobei R^2 eine gegebenenfalls substituierte Phenylgruppe der Formel



verkörpert, wobei R^a und R^b ausgewählt sind aus der Gruppe, bestehend aus Wasserstoffatomen, Halogenatomen, Alkylgruppen und/oder Alkoxygruppen.

12. Verbindung gemäß Anspruch 11, wobei R^a und R^b ausgewählt sind aus Halogenatomen.

13. Verbindung gemäß Anspruch 12, wobei R^2 eine 2,4-Difluorphenyl-, 4-Chlor-2-fluorphenyl- oder 4-Brom-2-fluorphenylgruppe ist.

14. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 3 und 5 bis 10, welche darstellt:

3-(2,4-Difluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Chlor-2-fluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Brom-2-fluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2,4-Difluorphenoxy)-6-ethyl-5-methyl-2-[(4-(methylsulfinylphenyl)]-4H-pyran-4-on;
3-(4-Fluor-2-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Chlor-2-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2-Chlor-4-methylphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2-Bromphenoxy)-6-methyl-2-[(4-methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(3-Bromphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Brom-2-chlorphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2,4-Dibromphenoxy)-6-methyl-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2,4-Difluorphenoxy)-6-methyl-2-[(4-ethylsulfinyl)phenyl]-4H-pyran-4-on;

6-Methyl-3-(2-methylphenoxy)-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
6-Methyl-3-(3-methylphenoxy)-2-[(4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(2-Fluor-4-methylphenoxy)-6-methyl-2-[(4-methylsulfinyl)phenyl]-4H-pyran-4-on;

Enantiomere davon, Mischungen davon und pharmazeutisch verträgliche Salze davon.

15. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 14, bei der das Schwefelatom der Sulfinylgruppe die (S)-Konfiguration besitzt.

16. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 14, bei der das Schwefelatom der Sulfinylgruppe die (R)-Konfiguration besitzt.

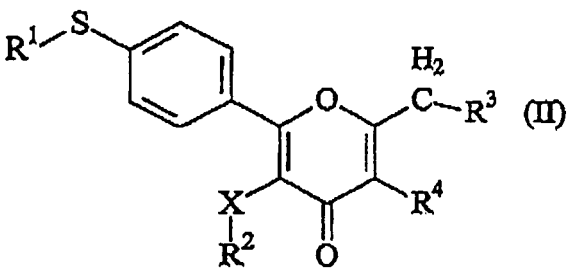
17. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 3 und 5 bis 10, die darstellt:

3-(2,4-Difluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Chlor-2-fluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on;
3-(4-Brom-2-fluorphenoxy)-6-methyl-2-[4-(methylsulfinyl)phenyl]-4H-pyran-4-on

in Form der Konfiguration der (-)-Enantiomere, Mischungen davon und pharmazeutisch verträgliche Salze davon.

18. Verfahren zur Herstellung einer Verbindung der Formel (I), wie in einem beliebigen der Ansprüche 1 bis 16 definiert, wobei das Verfahren umfasst:

(a) Umsetzen eines Mercaptoderivats der Formel (II):



(II)

worin R^1, R^2, R^3, R^4 und X wie in Anspruch 1 definiert sind mit einem Oxidationsmittel.

19. Verfahren gemäß Anspruch 18, wobei das Oxidationsmittel

(a) entweder Natriummetaperiodat ist, sofern racemische Sulfinylmischungen erhalten werden sollen; oder
(b) eine Mischung von Titantetraisopropoxid, t-Butylhydroperoxid und entweder der (R,R)- oder der (S,S)-Form von Diethyltartrat, wenn es erwünscht ist, eine enantiomerangereicherte Verbindung der Formel (I) zu erhalten.

20. Verfahren gemäß Anspruch 19, wobei die Reaktion in chlorierten Lösungsmitteln oder in einer Mischung chlorierter Lösungsmittel und C_1-C_4-Alkohole stattfindet.

21. Verfahren gemäß Anspruch 20, wobei das chlorierte Lösungsmittel ausgewählt ist aus 1,2-Dichlorethan, Methylenchlorid, Chloroform und Mischungen davon.

22. Pharmazeutische Zusammensetzung, umfassend eine Verbindung gemäß einem beliebigen der Ansprüche 1 bis 17 oder ein pharmazeutisch verträgliches Salz davon im Gemisch mit einem pharmazeutisch verträglichen Carrier oder Verdünnungsmittel.

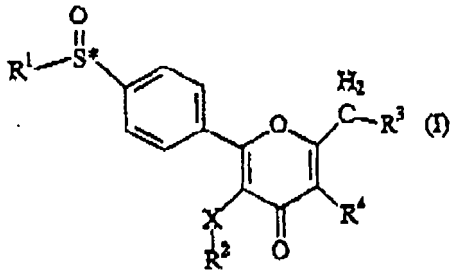
23. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 17 oder Zusammensetzung gemäß Anspruch 22 zur Verwendung in einem Behandlungsverfahren des menschlichen oder tierischen Körpers mittels Therapie.

24. Verwendung einer Verbindung gemäß einem beliebigen der Ansprüche 1 bis 17 oder eines pharmazeutisch verträglichen Salzes davon oder einer Zusammensetzung gemäß Anspruch 22 zur Herstellung eines Medikaments zur Verwendung in der Behandlung von Schmerz, Fieber oder Entzündung zur Inhibierung Prostanoid-induzierter Glatter-Muskel-Kontraktion oder zur Vorbeugung oder Behandlung von kolorektalem Krebs oder neurodegenerativen Krankheiten.

25. Verbindung gemäß einem beliebigen der Ansprüche 1 bis 17 oder Zusammensetzung gemäß Anspruch 22 zur Verwendung in der Behandlung von Schmerz, Fieber oder Entzündung zur Inhibierung Prostanoid-induzierter Glatter-Muskel-Kontraktion oder zur Vorbeugung oder Behandlung von kolorektalem Krebs oder neurodegenerativen Krankheiten.

Revendications

1. Composé de formule (I) :



dans laquelle

- R^1 représente un groupe alkyle;
- R^2 représente un groupe alkyle, cycloalkyle en C_3-C_7, pyridyle, thiényle, naphtyle, tétrahydronaphtyle ou indanyle, ou un groupe phényle qui peut être non substitué ou substitué par un ou plusieurs atomes d'halogène ou groupes alkyles, trifluorométhyles, hydroxy, alcoxy, méthylthio, amino, mono- ou dialkylamino, hydroxyalkyles ou hydroxycarbonyles ;
- R^3 et R^4, qui peuvent être identiques ou différents, représentent un atome d'hydrogène, ou un groupe alkyle, alcényle ou alcynyle qui peut être non substitué ou substitué par un ou plusieurs atomes d'halogène ;
- X représente une liaison simple, un atome d'oxygène ou un groupe méthylène ;
- lesdits groupes alkyles, ledit groupe cycloalkyle en C_3-C_7, ledit groupe alcoxy et les groupes alkyles contenus dans lesdits groupes monoalkylamino et dialkylamino sont chacun indépendamment non substitués ou substitués par 1, 2 ou 3 substituants qui peuvent être identiques ou différents et sont choisis parmi les atomes d'halogène, les groupes hydroxy et les groupes alcoxy ayant de 1 à 4 atomes de carbone, lesquels groupes alcoxy ayant de 1 à 4 atomes de carbone étant non substitués ou substitués par 1, 2 ou 3 substituants qui peuvent être identiques ou différents et sont choisis parmi les atomes d'halogène et les groupes hydroxy ; et
- lesdits groupes hydroxyalkyles sont des groupes hydroxyalkyle(C_1-C_{10}) et peuvent être substitués par un ou plusieurs radicaux hydroxyles ;

les énantiomères de celui-ci, les mélanges de celui-ci et des sels pharmaceutiquement acceptables de celui-ci.

2. Composé selon la revendication 1, dans lequel les groupes alkyles sont des groupes alkyles en C_1-C_{20}, les groupes alcoxy sont des groupes alcoxy en C_1-C_{10}, les groupes mono- ou dialkylamino sont des groupes mono- ou dialkyl(C_1-C_{10})amino, les groupes alcényles sont des groupes alcényles en C_2-C_{20} et les groupes alcynyles sont des groupes alcynyles en C_2-C_{20}.

3. Composé selon la revendication 1 ou la revendication 2, dans lequel R^1 représente un groupe alkyle non substitué.

4. Composé selon la revendication 3, dans lequel R^1 est un groupe méthyle.

5. Composé selon l'une quelconque des revendications 1 à 4, dans lequel X représente un atome d'oxygène.

6. Composé selon l'une quelconque des revendications 1 à 5, dans lequel R^3 et R^4 représentent un atome d'hydrogène ou un groupe alkyle en C_{1-3} non substitué.

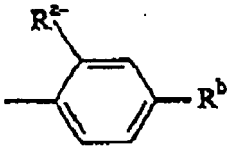
7. Composé selon la revendication 6, dans lequel R^3 et R^4 représentent un atome d'hydrogène.

8. Composé selon l'une quelconque des revendications 1 à 7, dans lequel R^2 est un groupe alkyle ramifié, cycloalkyle en C_3-C_7, naphtyle, tétrahydronaphtyle ou indanyle, un groupe phényle non substitué ou un groupe phényle substitué par un ou plusieurs atomes d'halogène, groupes alkyles et/ou groupes alcoxy.

9. Composé selon la revendication 8, dans lequel R^2 est un groupe phényle non substitué ou un groupe phényle substitué par 1, 2 ou 3 substituants indépendamment choisis parmi les atomes d'halogène, un groupe méthoxy ou les groupes méthyles.

10. Composé selon la revendication 9, dans lequel R^2 représente un groupe phényle substitué par 1 ou 2 substituants indépendamment choisis parmi les atomes d'halogène et les groupes méthyles.

11. Composé selon la revendication 8, dans lequel R^2 représente un groupe phényle facultativement substitué de formule



dans laquelle R^a et R^b sont choisis dans le groupe constitué par les atomes d'hydrogène, les atomes d'halogène, les groupes alkyles et/ou les groupes alcoxy.

12. Composé selon la revendication 11, dans lequel R^a et R^b sont choisis parmi les atomes d'halogène.

13. Composé selon la revendication 12, dans lequel R^2 est un groupe 2,4-difluorophényle, 4-chloro-2-fluorophényle ou 4-bromo-2-fluorophényle.

14. Composé selon l'une quelconque des revendications 1 à 3 et 5 à 10, qui est :

la 3-(2,4-difluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one
la 3-(4-chloro-2-fluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one
la 3-(4-bromo-2-fluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4H-pyran-4-one
la 3-(2,4-difluorophénoxy)-6-éthyl-5-méthyl-2-[(4-(méthylsulfinylphényl)]-4*H*-pyran-4-one ;
la 3-(4-fluoro-2-méthylphénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 3-(4-chloro-2-méthylphénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 3-(2-chloro-4-méthylphénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 3-(2-bromophénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)-phényl]-4*H*-pyran-4-one ;
la 3-(3-bromophénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)-phényl]-4*H*-pyran-4-one ;
la 3-(4-bromo-2-chlorophénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 3-(2,4-dibromophénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 3-(2,4-difluorophénoxy)-6-méthyl-2-[(4-(éthylsulfinyl)phényl]-4*H*-pyran-4-one ;
la 6-méthyl-3-(2-méthylphénoxy)-2-[(4-(méthylsulfinyl)-phényl]-4*H*-pyran-4-one ;
la 6-méthyl-3-(3-méthylphénoxy)-2-[(4-(méthylsulfinyl)-phényl]-4*H*-pyran-4-one ;
la 3-(2-fluoro-4-méthylphénoxy)-6-méthyl-2-[(4-(méthylsulfinyl)phényl]-4*H*-pyran- 4- one ;

les énantiomères de celui-ci, les mélanges de celui-ci et les sels pharmaceutiquement acceptables de celui-ci.

15. Composé selon l'une quelconque des revendications 1 à 14, dans lequel l'atome de soufre du groupe sulfinyle a la configuration (S).

16. Composé selon l'une quelconque des revendications 1 à 14, dans lequel l'atome de soufre du groupe sulfinyle a la

configuration (R).

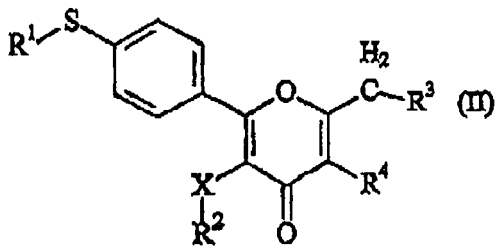
17. Composé selon l'une quelconque des revendications 1 à 3 et 5 à 10, qui est :

la 3-(2,4-difluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one
la 3-(4-chloro-2-fluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4*H*-pyran-4-one
la 3-(4-bromo-2-fluorophénoxy)-6-méthyl-2-[4-(méthylsulfinyl)phényl]-4H-pyran-4-one

sous la forme des énantiomères de configuration (-), de mélanges de celui-ci et de sels pharmaceutiquement acceptables de celui-ci.

18. Procédé pour préparer un composé de formule (I) tel que défini dans l'une quelconque des revendications 1 à 16, lequel procédé comprend :

(a) la réaction d'un dérivé mercapto de formule (II) :



(II)

dans laquelle R^1, R^2 , R^3, R^4 et X sont tels que définis dans la revendication 1, avec un agent oxydant.

19. Procédé selon la revendication 18, dans lequel l'agent oxydant est soit :

(a) du métaperiodate de sodium lorsque des mélanges sulfinylés racémiques doivent être obtenus ; soit
(b) un mélange de tétraisopropoxyde de titane, d'hydroperoxyde de t-butyle et des formes soit (R,R) soit (S,S) du tartrate de diéthyle lorsque l'on souhaite obtenir un composé de formule (I) enrichi énantiomériquement.

20. Procédé selon la revendication 19, dans lequel la réaction a lieu dans des solvants chlorés ou un mélange de solvants chlorés et d'alcools en C_1-C_4.

21. Procédé selon la revendication 20, dans lequel le solvant chloré est choisi parmi le 1,2-dichloroéthane, le chlorure de méthylène, le chloroforme et des mélanges de ceux-ci.

22. Composition pharmaceutique comprenant un composé selon l'une quelconque des revendications 1 à 17 ou un sel pharmaceutiquement acceptable de celui-ci, en mélange avec un véhicule ou diluant pharmaceutiquement acceptable.

23. Composé selon l'une quelconque des revendications 1 à 17 ou composition selon la revendication 22, pour utilisation dans un procédé de traitement du corps humain ou animal par thérapie.

24. Utilisation d'un composé selon l'une quelconque des revendications 1 à 17 ou d'un sel pharmaceutiquement acceptable de celui-ci ou d'une composition selon la revendication 22, pour la fabrication d'un médicament pour utilisation dans le traitement d'une douleur, d'une fièvre ou d'une inflammation pour inhiber une contraction de muscle lisse induite par prostanoïde ou pour la prévention ou le traitement d'un cancer colorectal ou de maladies neurodégénératives.

25. Composé selon l'une quelconque des revendications 1 à 17 ou composition selon la revendication 22, pour l'utilisation dans le traitement d'une douleur, d'une fièvre ou d'une inflammation pour inhiber une contraction de muscle lisse induite par prostanoïde ou pour la prévention ou le traitement d'un cancer colorectal ou de maladies neurodégénératives.

REFERENCES CITED IN THE DESCRIPTION

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