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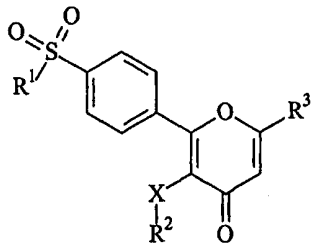

(I)

(57) Abstract

2–Phenylpyran–4–one derivatives of formula (I), wherein R^1 represents an alkyl or $-NR^4R^5$ group, wherein R^4 and R^5 each independently represents a hydrogen atom or 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 represents a methyl, hydroxymethyl, alkoxymethyl, C_3–C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2–R^6 group wherein R^6 represents an alkyl group; and X represents a single bond, an oxygen atom, a sulfur atom or a methylene group; or pharmaceutically acceptable salts thereof, processes for their production and synthetic intermediates used in said processes, pharmaceutical compositions containing them and their use in medical treatment.

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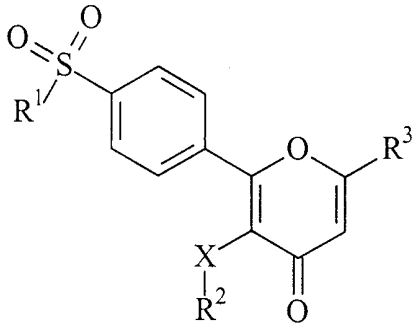
2-PHENYLPYRAN-4-ONE DERIVATIVES

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

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 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.

We have now found that certain 2-phenylpyran-4-one derivatives selectively inhibit COX-2 in preference to COX-1 and are useful in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever and asthma with fewer side effects.

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



(I)

wherein:

R^1 represents an alkyl or $-NR^4R^5$ group, wherein R^4 and R^5 each independently represents a hydrogen atom or 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 represents a methyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2-R^6 group wherein R^6 represents an alkyl group; and

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

or a pharmaceutically acceptable salt thereof.

The alkyl groups and moieties such as those present in the alkoxy, hydroxyalkyl, mono- or di-alkylamino groups, mentioned in relation to the groups R^1 to R^6 are usually "lower" alkyl that is containing from 1 to 6 particularly from 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight. Preferred alkyl groups, and where relevant alkyl moieties, include methyl, ethyl, propyl including i-propyl, and butyl including n-butyl, t-butyl and sec-butyl.

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. 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 or 3 and 5 positions.

In particular, it is preferred that R^2 represents a branched alkyl, C_3-C_7 (preferably C_3, C_5 or C_6) cycloalkyl, napthyl, tetrahydronaphthyl or indanyl group, an unsubstituted phenyl group or a phenyl group substituted by one or more

halogen atoms, alkoxy groups, preferably methoxy groups, and/or alkyl groups, preferably methyl groups. The phenyl group preferably has 1, 2 or 3 substituents, more preferably 1 or 2 substituents. Halogen atoms are preferably selected from fluorine, chlorine and bromine atoms. When R^2 is a phenyl group substituted by one or more halogen atoms, alkoxy groups and/or alkyl groups, preferably one of the substitutions is at the 4-position of the phenyl group. When R^2 is a phenyl group substituted by one or two halogen atoms at least one of the substitutions is preferably on the 2- or the 4-position.

It is preferred that R^1 independently represents an unsubstituted alkyl group such as methyl, ethyl, propyl or butyl, preferably methyl, or an NH_2 group (i.e. R^4 and R^5 in the above formula both independently represent an H atom).

It is also preferred that R^3 independently represents an unsubstituted alkyl group such as methyl, ethyl, propyl or butyl, preferably methyl, a nitrile group, a hydroxymethyl group, a methoxymethyl group, a difluoromethyl group or a hydroxycarbonyl group.

It is further preferred that X independently represents a single bond, an oxygen atom or a methylene group more preferably a single bond or an oxygen atom.

Specific examples of the 2-phenylpyran-4-one derivatives of the present invention include:

2-(4-methanesulfonylphenyl)-6-methyl-3-phenylpyran-4-one,

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl-6-methylpyran-4-one,

3-(3-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-bromophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

2-(4-methanesulfonylphenyl)-6-methyl-3-*p*-tolylpyran-4-one,

2-(4-methanesulfonylphenyl)-6-methyl-3-*m*-tolylpyran-4-one,

2-(4-methanesulfonylphenyl)-6-methyl-3-*o*-tolylpyran-4-one,

2-(4-methanesulfonylphenyl)-6-methyl-3-(4-trifluoromethylphenyl)pyran-4-one,

3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3,5-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2,5-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2,6-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3-fluoro-4-methoxyphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-chloro-3-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2-chloro-4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-cyclohexyl-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

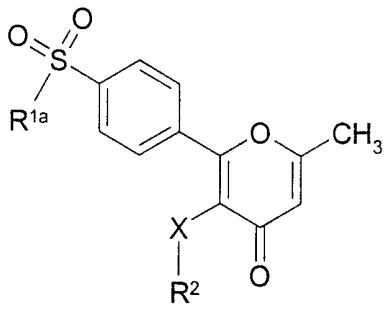
2-(4-methanesulfonylphenyl)-6-methyl-3-naphthalen-2-ylpyran-4-one,

4-(6-methyl-4-oxo-3-phenyl-4*H*-pyran-2-yl) benzenesulfonamide,
4-[3-(4-fluorophenyl)-6-methyl-4-oxo-4*H*-pyran-2-yl] benzenesulfonamide,
4-[3-(3,4-dichlorophenyl)-6-methyl-4-oxo-4*H*-pyran-2-yl] benzenesulfonamide,
5-(2,4-difluorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4*H*-pyran-2-carbonitrile.
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy) pyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,
and anyone of the compounds specifically identified in Table 4, and pharmaceutically acceptable salts thereof.

Of outstanding interest are:
3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

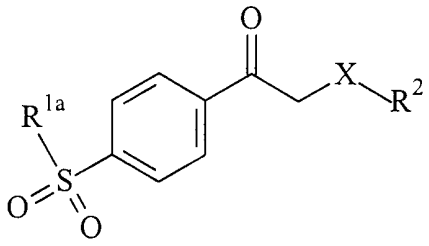
3-(4-bromophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy) pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxy-methylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonyl-phenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

The present invention also provides processes for preparing a compound of formula (I) which depend on the definition of R^3. When R^3 is a methyl group, compounds of formula (I) are prepared according to the definition of R^1. Thus, compounds of formula (I) in which R^3 is a methyl group and R^1 is an alkyl or $-NR^4R^5$ group in which R^4 and R^5 are alkyl groups, viz. a 2-phenylpyran-4-one derivative of formula (II):



(II)

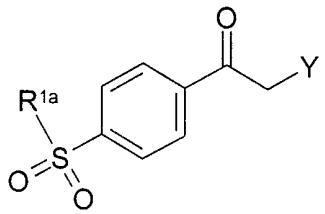
wherein R^{1a} is an alkyl or $-NR^{4a}R^{5a}$ group in which R^{4a} and R^{5a} are each independently alkyl groups, and R^2 and X are as defined above, which comprises reacting a carbonyl derivative of formula (III):



(III)

wherein R^{1a}, R^2 and X are as defined above with an excess of anhydrous acetic acid and polyphosphoric acid at a temperature from 100°C to 150°C.

The carbonyl derivative of formula (III) may be obtained by methods well known in the literature (EP-A-714883; WO96/06840; WO96/31509 and DE-2064520) or when X represents an oxygen or sulfur atom, by reacting a phenacyl derivative of formula (IV):



(IV)

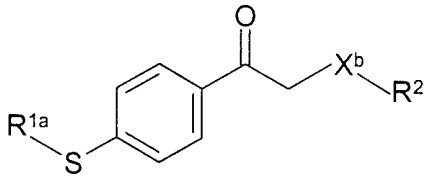
wherein R^{1a} is as defined above and Y represents a chlorine or bromine atom, with a hydroxy or mercapto derivative of formula (V):

$$HX^a - R^2 \qquad (V)$$

wherein R^2 is as defined above and X^a is an oxygen or sulfur atom.

The reaction between the phenacyl derivative of formula (IV) and the intermediate compound of formula (V) may be carried out by heating a mixture of these two starting materials, optionally in a solvent mixture of methylene chloride, benzene or toluene and water, at a temperature of from 15°C to 30°C and in the presence of a phase transfer catalyst as benzyltriethylamonium chloride.

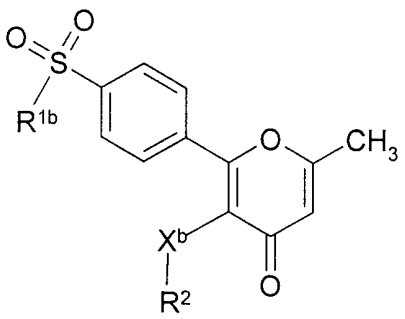
The carbonyl derivative of formula (III) in which X is other than a sulfur atom, may also be prepared by reacting a thio derivative of formula (VI):



(VI)

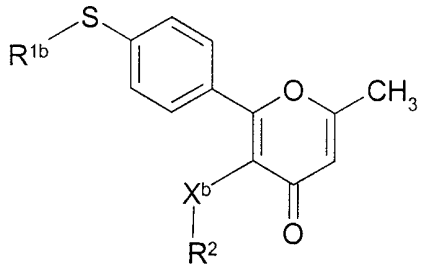
wherein R^{1a} and R^2 are as defined above, and X^b is a single bond, an oxygen atom or a methylene group, with an oxidizing agent, preferably magnesium monoperoxyphthalate or 3-chloroperoxybenzoic acid. The reaction is preferably carried out in an organic solvent such as a mixture of methylene chloride with methanol or ethanol, at a temperature of from 10°C to 40°C.

The present invention also provides a process for the preparation of a compound of formula (I) wherein R^3 is a methyl group, R^1 is an alkyl group, and X is other than a sulfur atom viz. 2-phenylpyran-4-one derivative of formula (VII):



(VII)

wherein R^{1b} is an alkyl group and R^2 and X^b are as defined above by reacting a mercapto derivative of formula (VIII):

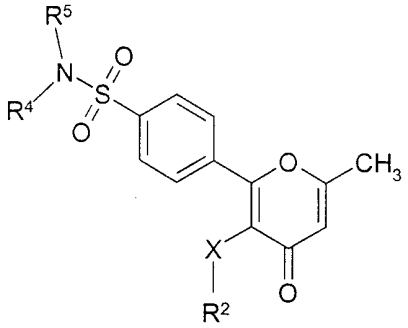


(VIII)

wherein R^{1b}, R^2 and X^b are as defined above with an oxidizing agent, preferably with magnesium monoperoxyphthalate or 3-chloroperoxybenzoic acid.

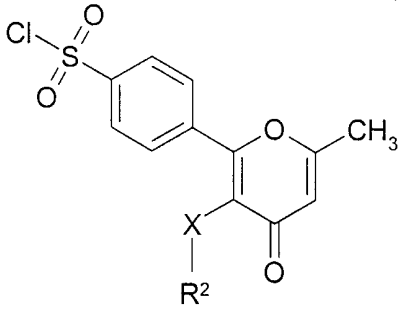
The reaction between the mercapto derivative of formula (VIII) and the oxidizing agent is preferably carried out, as previously disclosed for the compound of formula (VI), in an organic solvent such as a mixture of methylene chloride with methanol or ethanol, at a temperature of from 10°C to 40°C.

The present invention additionally provides a process for the preparation of a compound of formula (I) wherein R^1 is a -NR^4R^5 group and R^3 is a methyl group, viz. 2-phenylpyran-4-one derivative of formula (IX):



(IX)

wherein R^2, R^4, R^5 and X are as defined above by reacting a chlorosulfonyl derivative of formula (X):



(X)

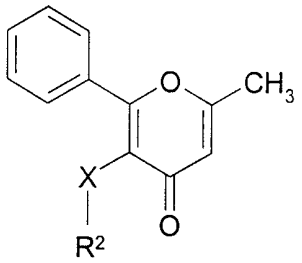
wherein R^2 and X are as defined above with an amine of formula (XI):

$$R^4\text{-}NH\text{-}R^5 \qquad (XI)$$

wherein R^4 and R^5 are as defined above.

This reaction is preferably carried out at a temperature of from 10°C to 40°C.

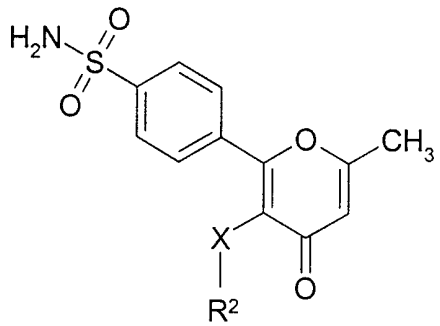
The chlorosulfonyl derivative of formula (X) may, for example, be prepared by reacting a compound of formula (XII):



(XII)

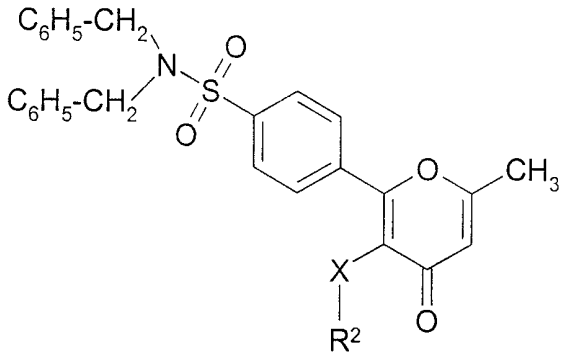
wherein R^2 and X are as defined above with chlorosulfonic acid, preferably at a temperature of from 80°C to 120°C.

The present invention further provides a process for the preparation of a compound of formula (I) wherein R^3 is a methyl group and R^1 is a $-NR^4R^5$ group wherein R^4 and R^5 are hydrogen, viz, the 2-phenylpyran-4-one derivative of formula (XIII):



(XIII)

wherein R^2 and X are as defined above by debenzylation of the corresponding N,N-dibenzyl derivative of formula (XIV):



(XIV)

wherein R^2 and X are as defined above.

The debenzylation is preferably carried out with an excess of trifluoroacetic, sulfuric or methanesulfonic acid at a temperature of from 0°C to 120°C.

The intermediate of formula (XIV) may be prepared according to the above processes using appropriate starting materials wherein R^4 and R^5 (or R^{4a} and R^{5a}) both represent benzyl groups.

The intermediate of formula (IV) and (VI) used in the preparation of the compounds of the invention may be prepared by methods disclosed in the literature, for example, in M.F. Saettone, J. Org. Chem. 31, p. 1959 (1966) and WO-9606840.

The intermediate compounds of formulae (VIII) and (XII) may be prepared by the same process disclosed for the preparation of compounds of formula (II), with the appropriate starting materials.

The 2-phenylpyran-4-one derivatives of formula (I) wherein R^3 is other than a methyl group, can be prepared by processes which are represented in the following scheme:

SCHEME

XV
XVI
XVII
XVIII
XIX
XX
XXI
XXII
XXIII
XXIV
XXV
Se O2
Ox.
NaH4B
SF4, HF
1) NH2OH
2) Ac2O
1) Ph3 P = R6
2) H2, Pd / C
Z - R7

As can be seen in the scheme, 2-phenylpyran-4-one derivatives of formula (I) wherein R^3 is other than a methyl group, viz. compounds of formulae (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) and (XXIV), are prepared from compounds of formula (I) in which R^3 is a methyl group, viz. compound of formula (XV), which processes of preparation have been disclosed above. In a first stage, compounds of formula (XV) are treated with an oxidizing agent as selenium dioxide in an organic solvent as tetrahydrofuran or dioxan, in a pressure vessel and at a temperature from 100°C to 190°C. The corresponding aldehyde of formula (XVI) is obtained, which is used as starting material to obtain the compounds of formula (I) with R^3 other than a methyl group.

The compounds of formula (I) wherein R^3 is a hydroxycarbonyl group, viz. compound of formula (XVII), are prepared from the corresponding aldehyde (XVI) by reaction with an oxidizing agent as pyridinium dichromate or manganese dioxide in an organic solvent as N,N-dimethylformamide or ethanol at a temperature between -5°C and 35°C. The obtained compounds (XVII) are used as starting materials to obtain compounds of formula (I) wherein R^3 is a trifluoromethyl group, viz. compound of formula (XVIII). The reaction is carried out by reaction of compounds (XVII) with a mixture of sulphur tetrafluoride and hydrogen fluoride, optionally in the presence of an organic solvent as methylene chloride, in a pressure vessel, and at a temperature from 20°C to 140°C.

The compounds of formula (I) wherein R^3 represents a hydroxymethyl group viz. compounds of formula (XIX) are prepared by reduction of compounds (XVI) with a boron or aluminium hydride, preferably sodium borohydride in a solvent as methanol or ethanol and at a temperature from 10°C to 40°C. Further reaction of compounds (XIX) with an appropriate halide of formula (XXIII):

$$Z - R^7 \qquad \text{(XXIII)}$$

wherein Z represents a chlorine, bromine or iodine atom and R^7

represents an alkyl, C_3-C_7 cycloalkyl or benzyl group, provide the compounds of formula (I) wherein R^3 is an alkoxymethyl, C_3-C_7 cycloalkoxymethyl or benzyloxymethyl group viz. compounds of formula (XX). The reaction is carried out in an organic solvent such as acetone, N,N-dimethylformamide or tetrahydrofuran in the presence of sodium or potassium hydride or amide, and at a temperature between 20°C and 120°C.

Also aldehydes of formula (XVI) are used as starting material to obtain compounds of formula (I) wherein R^3 is a nitrile group, viz. compounds of formula (XXI). The reaction is carried out in a first stage by treatment of aldehydes (XVI) with hydroxylamine hydrochloride and formic acid at a temperature from 80°C to 120°C. The resulting oxime derivative is isolated and heated with an excess of acetic anhydride at a temperature between 100°C to 180°C.

The compounds of formula (I) wherein R^3 represents a difluoromethyl group, viz. compounds of formula (XXII), are prepared from aldehydes of formula (XVI) by reaction with a fluorinated reagent as diethylaminosulfur trifluoride or a mixture of sulfur tetrafluoride-hydrogen fluoride, optionally in the presence of an organic solvent as methylene chloride, benzene or toluene and at a temperature from 0°C to 130°C.

The 2-phenylpyran-4-one derivatives of formula (I) in which R^3 is a CH_2-R^6 group, viz. compounds of formula (XXIV), are also prepared from aldehydes of formula (XVI) in a two stages process. In the first stage, the aldehyde (XVI) is reacted with a triphenylphosphine derivative (XXV) in the presence of a solvent as dioxane, dimethoxyethane or tetrahydrofuran at a temperature from 15°C to the boiling point of the solvent. The resulting compound is hydrogenated in the second stage of the process in the presence of a catalyst as palladium on activated carbon. The reaction is carried out in the presence of a solvent as methanol, ethanol or ethyl acetate at a temperature from 15°C to 40°C.

The 2-phenylpyran-4-one derivatives of formula (I) in which there is the presence of a basic group, can be converted by methods known per se into pharmaceutically acceptable salts,

preferably acid addition salts by treatment with organic or inorganic acids as fumaric, tartaric, succinic or hydrochloric acid. Also, 2-phenylpyran-4-one derivatives of formula (I) in which R^3 represents an hydroxycarbonyl group, may be converted into pharmacologically acceptable salts with, for instance, alkali metals such as sodium or potassium by reaction with an alkali metal hydroxide.

The following biological tests and data further illustrate this invention.

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 µl aliquots of blood were incubated with either 5 µl vehicle (dimethylsulphoxide) or 5 µl of a test compound for 1 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 (ELISA). The effect of the compounds were 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.

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 (ELISA). The effects of inhibitors were 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_{50} values were obtained by non-linear regression using InPlot, GraphPad software on an IBM

computer.

Anti-inflammatory activity (adjuvant arthritis)

Male Wistar rats weighing 175-200 g with free access to food and water were used. On day 0, the animals received an intraplantar injection of a suspension of Mycobacterium tuberculosis in paraffin oil (0.5 mg/rat) on the left hind paw. A group of nonarthritic control rats were injected with paraffin oil alone. On days 11 and 14 after induction of arthritis, the volume of the hind paw of each rat was measured using a water plethysmograph. Animals whose paw volumes increased during that time were selected. Rats were distributed into groups of 8 having equal mean paw volumes and an approximately equal standard deviation.

Test compounds were administered p.o. once daily for 7 days (days 14-20). Nonarthritic and arthritic control rats received vehicle alone for 7 days. The hind paw volumes were measured 20 h after the last dose (on day 21). The body weight was determined every second day.

The results were expressed as the percentage of inhibition of inflammation (paw volume) for each treatment group, considering both the arthritic and nonarthritic vehicle controls. The ANOVA tests was used for statistical studies.

Ulcerogenic activity

Animals : Male Wistar rats (Interfauna, U.K., Ltd.) weighing about 150-175 g were used. Animals were maintained on a 12:12 hour light-dark cycle (lights on at 7:00 am) at room temperature (22±1°C). Food and water were allowed *ad libitum*.

Procedure : The compounds were administered by the oral route once a day for 4 consecutive days. The body weight of each rat was assessed every day before drug administration. The animals were anesthesized 24 h after the last dosing and 1 ml of blood was extracted by cardiac puncture using heparin (10 U/ml) as anticoagulant. The percentage of hematocrit was measured. The intestines were removed, opened longitudinally

and gently washed. The macroscopic severity of the intestinal erosions was assessed using a parametric scale, evaluating the number of the perforated and non-perforated intestinal ulcers by means of a lesion index ranging from 0 to 3 (0:no ulcers, 1:<10 ulcers, 2:10-25 ulcers to 3:>25 ulcers). No gastric ulcers are observed using this protocol.

The treatments were randomized in each experiment. The results were compared with those obtained in the vehicle-treated group using the ANOVA test.

Results

The results obtained from the biological assays are shown in Table 1, 2 and 3.

TABLE 1: COX-1 and COX-2 Inhibition

Compound (*)	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	Ratio COX-1/COX-2
Indomethacin	0.19	0.22	0.86
2	>100	1.06	>94
4	>100	1.5	>66
5	>100	2.1	>47
8	>100	1.7	>58
15	100	1.1	90
22	37.1	0.7	53
31	>100	1.67	>59
37	>100	1.08	>92
39	>100	0.96	>104
40	27	0.14	193
41	>100	0.35	>285
42	41	0.2	205
43	>100	0.8	125

Compound (*)	COX-1 IC_{50} (μM)	COX-2 IC_{50} (μM)	Ratio COX-1/COX-2
44	39	0.21	185
45	22	0.15	147
47	57.1	0.8	71
63	44	1.73	25
67	>100	2.1	>47

(*) See structures in Table 4.

Indomethacin is 1-(4-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.

TABLE 2: Anti-inflammatory activity

Compound	% Inhibition (dose, mg/kg)
Indomethacin	64 (1)
5	50 (1)
22	69 (1)
39	75 (1)
41	71 (1)
45	74 (1)

TABLE 3: Ulcerogenic activity

Compound	Dose (mg/kg)	Lesion index		Hematocrit (%)
		PU	NPU	
Vehicle		0	0	44.3±0.2
Indomethacin	10	3	3	22.7±1.6
5	100	0	0	44.1±0.7
22	100	0	0	44.4±0.3

Compound	Dose (mg/kg)	Lesion index		Hematocrit (%)
		PU	NPU	
39	100	0	0	43.7±0.4
41	100	0	0	43.4±1.9
45	100	0	0	44.4±0.9

PU: perforated ulcers, NPU: non-perforated ulcers.

As shown in Table 1, the 2-phenylpyran-4-one derivatives of formula (I) are potent and selective COX-2 inhibitors whereas the reference compound indomethacin is as equipotent as COX-2 and COX-1 inhibitor. Due to their low COX-1 inhibitory activity, the compounds of formula (I) present an important anti-inflammatory activity (see Table 2) and the benefit of significantly less harmful side effects than the non-steroidal anti-inflammatory drugs commonly used (e.g. gastrointestinal toxicity (see Table 3), renal side-effects, reduced effect on bleeding times and asthma induction in aspirin-sensitive subjects).

Thus the compounds of the invention are preferably selective inhibitors of mammalian COX-2, for example human COX-2. 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.

Preferred compounds of the invention have an IC_{50} value for COX-2 of less than 5 μM, preferably less than 3 more preferably less than 2.5 μM. Preferred compounds of the invention also have an IC_{50} value for COX-1 of greater than 10 μM, preferably greater than 20 μM. 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 greater than 20, 30 or 50, more preferably greater than 80, 90 or 100.

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 of colorectal cancer or neurodegenerative diseases.

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 of colorectal cancer or neurodegenerative diseases.

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 and bone resorption. 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 of colorectal cancer.

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.

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 bowl 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.

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, myocardial ischaemia and stroke.

Compounds of the present invention are inhibitors of cyclooxygenase-2 enzyme and are thereby useful to treat the cyclooxygenase-2 mediated diseases enumerated above. These compounds can further be used for the prevention of neurodegenerative diseases such as Alzheimer's disease.

Accordingly, the 2-phenylpyran-4-one derivatives of formula (I) 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 a 2-phenylpyran-4-one derivative of formula (I) or a pharmaceutically acceptable salt thereof.

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.

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

The pharmaceutically acceptable excipients which are admixed with the active compound, or salts of such 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.

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.

The diluents which may be used in the preparation of the compositions include those liquid and solid diluents which 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.

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.

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.

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.

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

EXAMPLE 1

a) To a solution of 2-(4-fluorophenyl)-1-(4-methanesulfonylphenyl)ethanone (1 g; 3.4 moles) in glacial acetic acid (15 ml), polyphosphoric acid (10 g) was added and then heated at 140°C for 16 hours. After cooling, the reaction was poured into ice-water, extracted with ethyl acetate (2 x 50

ml), the organic solution 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 as eluent. 3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one was obtained (0.5 g) m.p. 237°C (Compound 2 in Table 4).

EXAMPLE 2

a) To a solution of 2,4-difluorophenol (3.71 g; 29 mmol) and 2-bromo-1-(4-methylsulfanylphenyl)ethanone (7.00 g; 29 mmol) in methylene chloride (50 ml) was added a solution of potassium carbonate (5.91 g; 43 mmol) and tetrabutylammonium hydrogensulfate (0.48 g; 1.4 mmol) in water (20 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-methylsulfanyl-phenyl)ethanone was obtained (6.60 g), m.p. 70-71°C.

b) To a solution of 2-(2,4-difluorophenoxy)-1-(4-methyl-sulfanylphenyl)ethanone (6.60 g; 22 mmol) in methylene chloride (100 ml), water (20 ml) and 80% magnesium monoperoxyphatlate hexahydrate (15.26 g; 25 mmol) were added. The mixture was stirred at room temperature for 16 hours. The reaction was poured into saturated solution of sodium bicarbonate (200 ml) and extracted with methylene chloride (3 x 100 ml). The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. 2-(2,4-Difluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone was obtained (4.97 g) as a solid, m.p. 161-163°C.

c) To a solution of 2-(2,4-Difluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (4.60 g; 14 mmol) in acetic acid (70 ml), polyphosphoric acid (45 g) was added and then heated at 140°C for 5 hours. After cooling, the reaction was poured into ice-water, extracted with ethyl acetate (2 x 100 ml), the organic solution 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 (1:2) as eluent. Recrystallization from ethanol gave 3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (0.64 g), m.p. 191°C (Compound 45 in Table 4).

EXAMPLE 3

a) A solution of 4-(dibenzylsulfamoyl)benzoic acid (24 g; 63 mmoles) in thionyl chloride (50 ml) was boiled under reflux for 2.5 hours and the excess of thionyl chloride removed under reduced pressure. 4-(dibenzylsulfamoyl)benzoyl chloride (25 g) was obtained as an oil which was used in the next step without purification.

b) To a solution of N,O-dimethylhydroxylamine hydrochloride (7.37 g; 75.6 mmoles) and triethylamine (21.8 ml; 151 mmoles) in methylene chloride (150 ml), another solution of 4-(dibenzylsulfamoyl)benzoyl chloride (25 g) in methylene chloride (150 ml) was slowly added and the resulting mixture stirred at room temperature for 16 hours. The solid was filtered off, the solvent removed under reduced pressure and the residual oil purified by column chromatography with silica gel and n-hexane-ethyl acetate 1:1 as eluent. N,O-dimethylamide of 4-(dibenzylsulfamoyl)benzoic acid (22 g) was obtained, m.p. 75°C.

c) To a suspension of magnesium (2 g; 82.4 mmoles) in anhydrous tetrahydrofuran (20 ml), another solution of benzyl chloride (10.4 g; 82.4 mmoles) in anhydrous tetrahydrofuran (100 ml) was slowly added. When the reaction was completed, a solution of N,O-dimethylamide of 4-(dibenzylsulfamoyl)benzoic acid (7 g; 16.5 mmoles) in anhydrous tetrahydrofuran (50 ml) was slowly added while the temperature was maintained at 0°C. After stirring at the same temperature for half an hour, the reaction mixture was poured into an ammonium chloride saturated solution (100 ml), extracted with ethyl ether (3 x 75 ml) and the organic extracts dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual oil was purified by column chromatography with silica gel and n-hexane-ethyl acetate 1:3 as eluent. N,N-dibenzyl-4-

phenylacetylbenzesulfonamide (9.4 g) was obtained, m.p. 143°C.

d) To a solution of the above compound obtained in c) (9.4 g; 20.7 mmoles) in glacial acetic acid (140 ml), polyphosphoric acid (94 g) was added and the resulting mixture heated to 140°C for 16 hours. After cooling, the reaction mixture was poured into ice-water, extracted with ethyl acetate (3 x 150 ml) and the organic solution dried (Na_2SO_4). The solvent was removed in vacuo and to the residual oil, concentrated sulfuric acid (38 ml) was added, then stirred at 0°C for 10 minutes, further 60 minutes at room temperature and poured into ice-water. The precipitated solid was collected by filtration and purified by column chromatography with silica gel and ethyl acetate as eluent. 4-(6-methyl-4-oxo-3-phenyl-4H-pyran-2-yl)benzenesulfonamide (1.5 g) was obtained, m.p. 218°C (Compound 54 in Table 4).

EXAMPLE 4

a) To a solution of 3,4-dichlorophenylacetophenone (5.3 g; 20 mmoles) in glacial acetic acid (90 ml), polyphosphoric acid (64 g) was added and the resulting solution heated at 140°C for 24 hours. After cooling, the reaction mixture was poured into ice-water, extracted with ethyl acetate (3 x 75 ml), the organic solution dried (Na_2SO_4) and the solvent removed under reduced pressure. The obtained residue was purified by column chromatography with silica gel and n-hexane-ethyl acetate 3:2 as eluent. 3-(3,4-dichlorophenyl)-2-phenyl-6-methylpyran-4-one (1.68 g) was obtained, m.p. 104°C.

b) A solution of the compound obtained above (1.4 g; 4.3 mmoles) in chlorosulfonic acid (12 ml) was heated at 70°C for 1.5 hours and after cooling, the reaction mixture was slowly poured into ice-water and extracted with ethyl acetate (2 x 50 ml). The organic solution was dried (Na_2SO_4), the solvent removed under reduced pressure and to the residual oil, previously solved in methanol (10 ml), a saturated solution of ammoniac in methanol (40 ml) was slowly added. After stirring at room temperature for 1 hour, the solvent was removed under reduced pressure, the residue solved in ethyl acetate (100 ml)

and the resulting solution was washed with water (2 x 100 ml), dried (Na_2SO_4) and the solvent removed under reduced pressure. The residual oil was purified by column chromatography with silica gel and n-hexane-ethyl acetate 1:1 as eluent. 4-[3-(3,4-dichlorophenyl)-6-methyl-4-oxo-4H-pyran-2-yl]benzenesulfonamide (0.5 g) was obtained, m.p. 128°C (Compound 56 in Table 4).

EXAMPLE 5

a) To a solution of N,N-dibenzyl-4-(2-bromoacetyl)benzenesulfonamide (10.5 g, 23 mmoles), and p-chlorophenol (2.94 g, 23 mmoles) in methylene chloride (42 ml),potassium carbonate (4.83 g, 34.7 mmoles) and tetrabutylammonium bromide (0.42 g, 1.2 mmoles) in water (140 ml)was added. The reaction mixture was refluxed for 16 hours. After cooling, the mixture was diluted with methylene chloride (150 ml). The organic layer was separated, washed with water, and dried (Na_2SO_4). The solvent was removed under reduced pressure. N,N-dibenzyl-4-[2-(4-chlorophenoxy)acetyl]benzenesulfonamide (11.7 g) was obtained as a semisolid residue, which was used in the next step without further purification.

b) To a solution of N,N-dibenzyl-4-[2-(4-chlorophenoxy)acetyl]benzenesulfonamide (11.7 g, 23 mmoles) in acetic acid(105 ml), polyphosphoric acid (75 g) was added and the resulting solution was heated at 140°C for 5 hours. After cooling, the reaction mixture was poured into ice-water, extracted with ethyl acetate (3 x 150 ml), and the organic solution was dried (Na_2SO_4). The solvent was removed under reduced pressure and the resulting oil was solved in H_2SO_4 (33 ml). The mixture was stirred at room temperature for 15 minutes, and poured into ice-water. The solid was filtered off and purified by column chromatography with silica gel and ethyl acetate/methylene chloride/acetic acid (78:10:1) as eluent. 4-[3-(4-chlorophenoxy)-6-methyl-4-oxo-4H-pyran-2-yl] benzenesulfonamide (0.28 g) was obtained. m.p. 221°C (Compound 57 in Table 4).

EXAMPLE 6

a) To a solution of 3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (1.7 g; 4.5 mmoles) (compound 13) in dioxane (45 ml), selenium dioxide (2.2 g; 20 mmoles) was added and the mixture heated in a pressure vessel at 180°C for 1 hour. After cooling, the reaction mixture was filtered, the solvent removed under reduced pressure and the residual oil purified by column chromatography with silica gel and ethyl acetate as eluent. 5-(2,4-difluorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde (0.85 g) was obtained.

b) To a solution of the above compound (0.8 g; 2.1 mmoles) in formic acid (6 ml), hydroxylamine hydrochloride (0.17 g; 2.7 mmoles) was added and the mixture heated at 100°C for 2 hours. After cooling, the reaction mixture was poured into ice, 2N sodium hydroxide was added until pH=7 and extracted with ethyl acetate (2 x 50 ml). The organic solution was dried (Na_2SO_4) the solvent removed in vacuo and the residue was dissolved in acetic anhydride (15 ml) and heated at 150°C for 3 hours. The solvent was removed under reduced pressure, the residue treated with methylene chloride (50 ml) and the resulting solution washed with 2N sodium hydroxide (2 x 25 ml). The organic solution was dried (Na_2SO_4), the solvent removed in vacuo and the residue purified by column chromatography with silica gel and n-hexane-ethyl acetate 1:1 as eluent. 5-(2,4-difluorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbonitrile (0.2 g), m.p. 113°C (Compound 59 in Table 4).

EXAMPLE 7

a) To a solution of 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (4.0 g, 10.6 mmoles) in dioxane (50 ml), selenium dioxide (5.9 g, 53 mmoles) was added and heated into a sealed tube at 180°C for 30 minutes. After cooling, the raw material was filtered through Celite and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:1) as eluent. 5-(4-chlorophenyl)-6-

(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde (1.80 g) was obtained.

b) To a solution of 5-(4-chlorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde (1.8 g, 4.6 mmoles) in methanol (30 ml), sodium borohydride (0.26 g, 6.9 mmoles)was slowly added at 0°C. The resulting mixture was stirred for 30 minutes at room temperature. The reaction mixture was concentrated and the residue was solved in ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent. 3-(4-chlorophenyl)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (0.9 g) was obtained. m.p. 120°C. (Compound 60 in Table 4).

EXAMPLE 8

a) To a solution of 3-(4-chlorophenyl)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (0.5 g, 1.3 mmoles) in methylene chloride (10 ml), methyl iodide (0.24 ml, 3.86 mmoles),and a solution of sodium hydroxide (0.41 g, 10.3 mmoles) and tetrabutylammonium chloride (50 ml) in water (0.8 ml) were added. The reaction mixture was stirred at room temperature for 18 hours. The organic layer was diluted with methylene chloride (20 ml), washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure. The resulting solid was purified by column chromatography with silica gel and ethyl acetate as eluent. 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one (0.15 g) was obtained. m.p. 162°C (Compound 63 in Table 4).

EXAMPLE 9

a) To a solution of silver nitrate (0.88 g, 5.1 mmoles) in water (4 ml), a solution of sodium hydroxide (0.42 g, 6.2 mmoles) in water (4 ml) was added. The reaction mixture was stirred for 15 minutes at room temperature, and a solution 5-(4-chlorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-

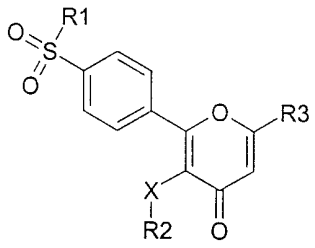
carbaldehyde in tetrahydrofuran (10 ml) was added. The reaction mixture was stirred for 3 hours at room temperature and filtered through Celite. The solvent was removed under reduced pressure and the residue was solved in ethyl acetate. The organic layer was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure. The resulting solid was purified by column chromatography with silica gel and ethyl acetate/methylene chloride/acetic acid (78:10:1) as eluent. 5-(4-chlorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid (0.13 g) was obtained. m.p. 236°C (Compound 65 in Table 4).

EXAMPLE 10

a) To a solution of 5-(4-chlorophenyl)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde (0.74 g, 1.9 mmoles) in methylene chloride (10 ml), diethylaminosulfide DAST (0.61 g, 3.8 mmoles) was slowly added at 0°C. The reaction mixture was stirred at this temperature for 1 hour and at room temperature for 16 hours. The mixture was diluted with methylene chloride (10 ml). The organic phase was washed with water, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent. 3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one (0.1 g) was obtained. m.p. 168-170°C (Compound 67 in Table 4).

The 2-phenylpyran-4-one derivatives of general formula (I) included in Table 4 were prepared according to the processes disclosed in these Examples, but with the appropriate starting materials.

TABLE 4



Compound	R1	X	R2	R3	Method Example	Melting Point (°C)
1	CH_3	single bond	C_6H_5	CH_3	1	185
2	CH_3	"	4-FC_6H_4	CH_3	1	237
3	CH_3	"	3-FC_6H_4	CH_3	1	182
4	CH_3	"	2-FC_6H_4	CH_3	1	136-137
5	CH_3	"	4-ClC_6H_4	CH_3	1	182
6	CH_3	"	3-ClC_6H_4	CH_3	1	131
7	CH_3	"	2-ClC_6H_4	CH_3	1	148
8	CH_3	"	4-BrC_6H_4	CH_3	1	198
9	CH_3	"	3-BrC_6H_4	CH_3	1	178
10	CH_3	"	4-$CH_3C_6H_4$	CH_3	1	205
11	CH_3	"	3-$CH_3C_6H_4$	CH_3	1	126
12	CH_3	"	2-$CH_3C_6H_4$	CH_3	1	91-93
13	CH_3	"	4-$CF_3C_6H_4$	CH_3	1	172
14	CH_3	"	2,3-diFC_6H_3	CH_3	1	187
15	CH_3	"	2,4-diFC_6H_3	CH_3	1	208
16	CH_3	"	3,4-diFC_6H_3	CH_3	1	207
17	CH_3	"	3,5-diFC_6H_3	CH_3	1	210
18	CH_3	"	2,5-diFC_6H_3	CH_3	1	183
19	CH_3	"	2,6-diFC_6H_3	CH_3	1	206

Compound	R1	X	R2	R3	Method Example	Melting Point (°C)
20	CH_3	"	2,3-diClC_6H_3	CH_3	1	200
21	CH_3	"	2,4-diClC_6H_3	CH_3	1	203
22	CH_3	"	3,4-diClC_6H_3	CH_3	1	156
23	CH_3	single bond	2,5-diClC_6H_3	CH_3	1	230
24	CH_3	"	2,6-diClC_6H_3	CH_3	1	186
25	CH_3	"	6-F,2-ClC_6H_3	CH_3	1	177
26	CH_3	"	2-F,4-ClC_6H_3	CH_3	1	171
27	CH_3	"	4-F,2-ClC_6H_3	CH_3	1	113
28	CH_3	"	4-Cl,3-$CH_3C_6H_3$	CH_3	1	98-99
29	CH_3	"	3-Cl,4-$CH_3C_6H_3$	CH_3	1	176
30	CH_3	"	3-F,4-$CH_3OC_6H_3$	CH_3	1	137
31	CH_3	"	3-Cl,4-$CH_3OC_6H_3$	CH_3	1	116
32	CH_3	"	i-C_3H_7	CH_3	1	108
33	CH_3	"	C_6H_{11} (cyclohexyl)	CH_3	1	98-99
34	CH_3	"	2-naphthyl	CH_3	1	122-123
35	CH_3	"	2-indanyl	CH_3	1	169
36	CH_3	"	2-tetra-hydronaphthyl	CH_3	1	103
37	CH_3	CH_2	C_6H_5	CH_3	1	137
38	CH_3	O	C_6H_5	CH_3	2	169
39	CH_3	O	4-FC_6H_4	CH_3	2	189
40	CH_3	O	2-FC_6H_4	CH_3	2	178

Compound	R1	X	R2	R3	Method Example	Melting Point (°C)
41	CH_3	O	4-ClC_6H_4	CH_3	2	196
42	CH_3	O	2-ClC_6H_4	CH_3	2	198
43	CH_3	O	4-BrC_6H_4	CH_3	2	188
44	CH_3	O	4-$CH_3C_6H_4$	CH_3	2	183
45	CH_3	O	2,4-diFC_6H_3	CH_3	2	191
46	CH_3	O	3,4-diFC_6H_3	CH_3	2	194
47	CH_3	O	2,5-diFC_6H_3	CH_3	2	189
48	CH_3	O	2,6-diFC_6H_3	CH_3	2	169
49	CH_3	O	3,4-diClC_6H_3	CH_3	2	177
50	CH_3	O	2,6-diClC_6H_3	CH_3	2	170
51	CH_3	O	4-Cl,3-$CH_3C_6H_3$	CH_3	2	183
52	CH_3	O	2,3,6-triClC_6H_2	CH_3	2	216
53	CH_3	O	2,4,6-triClC_6H_2	CH_3	2	171
54	NH_2	single bond	C_6H_5	CH_3	3	218
55	NH_2	"	4-FC_6H_4	CH_3	3	247
56	NH_2	"	3,4-diClC_6H_3	CH_3	4	128
57	NH_2	O	4-ClC_6H_4	CH_3	5	221
58	CH_3	single bond	4-ClC_6H_4	CN	6	189
59	CH_3	"	2,4-diFC_6H_3	CN	6	113
60	CH_3	"	4-ClC_6H_4	CH_2OH	7	120
61	CH_3	"	4-BrC_6H_4	CH_2OH	7	128-129
62	CH_3	"	2,4-diFC_6H_3	CH_2OH	7	173-175

Compound	R1	X	R2	R3	Method Example	Melting Point (°C)
63	CH_3	"	4-ClC_6H_4	CH_2O-CH_3	8	162
64	CH_3	"	2,4-diFC_6H_3	CH_2O-CH_3	8	184
65	CH_3	"	4-ClC_6H_4	COOH	9	236
66	CH_3	"	2,4-diFC_6H_3	COOH	9	241
67	CH_3	"	4-ClC_6H_4	CF_2H	10	168-170

Examples 11 and 12 illustrate pharmaceutical compositions according to the present invention and procedure for their preparation.

EXAMPLE 11

25,000 capsules each containing 100 mg of 3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (active ingredient) were prepared according to the following formulation:

Active ingredient	2.5 Kg
Lactose monohydrate	5 Kg
Colloidal silicone dioxide	0.05 Kg
Corn starch	0.5 Kg
Magnesium stearate	0.1 Kg

Procedure

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 12

100,000 Tablets each containing 50 mg of the 3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (active ingredient) were prepared from the following formulation:

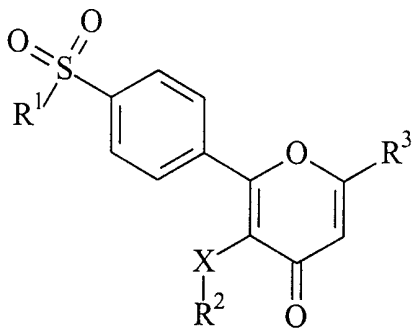
Active ingredient	5 Kg
Spray dried lactose	19.9 Kg
Microcrystalline cellulose	3.9 Kg
Sodium stearyl fumarate	0.2 Kg
Colloidal silicon dioxide	0.2 Kg
Carboxymethyl starch	0.8 Kg

Procedure

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):



(I)

wherein:

R^1 represents an alkyl or $-NR^4R^5$ group, wherein R^4 and R^5 each independently represents a hydrogen atom or 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 represents a methyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2-R^6 group wherein R^6 represents an alkyl group; and

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

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 represents an unsubstituted alkyl group or NH_2, R^2 represents 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, R^3 represents an unsubstituted alkyl group, a nitrile group, a hydroxymethyl group, a

methoxymethyl group, a difluoromethyl group or a hydroxycarbonyl group and X represents a single bond, an oxygen atom or a methylene group.

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

4. A compound according to any one of claims 1 to 3 wherein R^2 represents a phenyl group substituted by 1, 2 or 3 substituents independently selected from halogen atoms, methoxy groups and methyl groups, one of the substituents being on the 4-position.

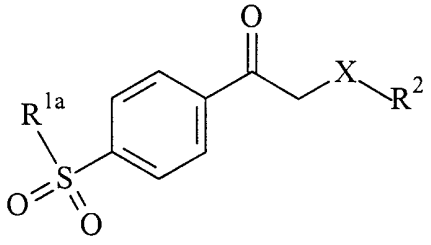
5. A compound according to any one of claims 1 to 3 wherein R^2 represents a phenyl group substituted by one or two halogen atoms at least one of which is on the 4-position or the 2-position.

6. 3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,

3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methyl phenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonyl-phenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

7. A process for the preparation of a compound of formula (I) as defined in any one of the preceding claims which process comprises:

(a) wherein R^1 is an alkyl or $-NR^4R^5$ group in which R^4 and R^5 each independently is an alkyl group, R^3 is a methyl group and R^2 and X are as defined in any one of claims 1 to 5, reacting a carbonyl derivative of formula (III):

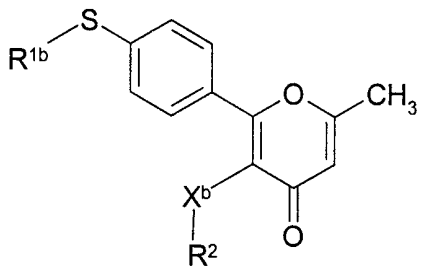


(III)

wherein R^{1a} is an alkyl or a $-NR^{4a}R^{5a}$ group in which R^{4a} and R^{5a}

are each independently alkyl groups and R^2 and X are as defined in any one of claims 1 to 5, with an excess of anhydrous acetic acid and polyphosphoric acid at a temperature from 100°C to 150°C;

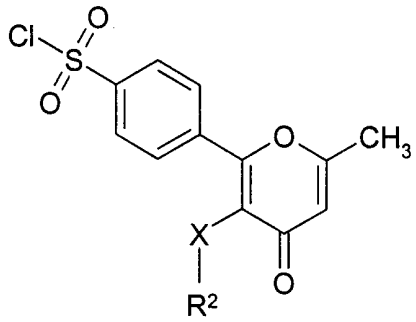
(b) wherein R^1 is an alkyl group, R^3 is a methyl group, X is as defined in any one of claims 1 to 5 with the proviso that it is other than a sulfur atom and R^2 is as defined in any one of claims 1 to 5, reacting a mercapto derivative of formula (VIII):



(VIII)

wherein R^{1b} is an alkyl group, X^b is as defined for X in any one of claims 1 to 5 with the proviso that it is other than a sulfur atom and R^2 is as defined in any one of claims 1 to 5, with an oxidizing agent;

(c) wherein R^1 is a $-NR^4R^5$ group, R^3 is a methyl group and R^2, R^4, R^5 and X are as defined in any one of claims 1 to 5, reacting a chlorosulfonyl derivative of formula (X):



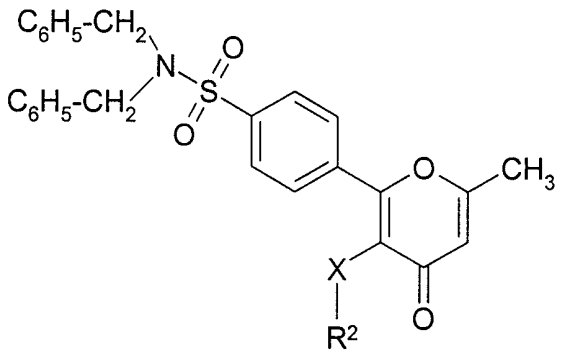
(X)

wherein R^2 and X are as defined in any one of claims 1 to 5, with an amine of formula (XI):

$$R^4\text{-}NH\text{-}R^5 \qquad \text{(XI)}$$

wherein R^4 and R^5 are as defined in any one of claims 1 to 5; or

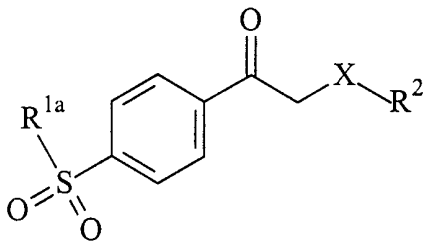
(d) wherein R^1 is a $-NR^4R^5$ group wherein R^4 and R^5 are hydrogen, R^3 is a methyl group and R^2 and X are as defined in any one of claims 1 to 5, by debenzylation of the corresponding N,N-dibenzyl derivative of formula (XIV):



(XIV)

wherein R^2 and X are as defined in any one of claims 1 to 5.

8. A compound of formula (III):



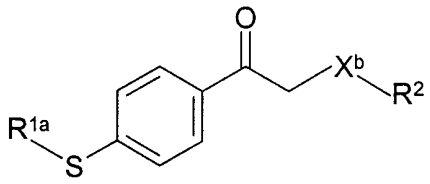
(III)

wherein R^{1a} is an alkyl or $-NR^{4a}R^{5a}$ group in which R^{4a} and R^{5a} are each independently alkyl groups, and R^2 and X are as defined in any one of claims 1 to 5.

9. A compound according to claim 8 wherein R^{1a} is a methyl group, X is an oxygen atom and R^2 is selected from phenyl, 4-fluorophenyl, 2-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 4-methylphenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 4-chloro-3-methylphenyl, 2,3,6-trichlorophenyl and 2,4,6-

trichlorophenyl.

10. A compound of formula (VI):



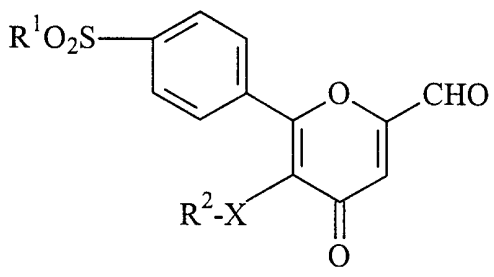
(VI)

wherein R^{1a} is an alkyl or $-NR^{4a}R^{5a}$ group in which R^{4a} and R^{5a} are each independently alkyl groups, X^b is as defined for X in any one of claims 1 to 5 with the proviso that it is other than a sulfur atom and R^2 is as defined in any one of claims 1 to 5.

11. A compound according to claim 10 wherein R^{1a} is a methyl group, X is an oxygen atom and R^2 is selected from phenyl, 4-fluorophenyl, 2-fluorophenyl, 4-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 4-methylphenyl, 2,4-difluorophenyl, 3,4-difluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 3,4-dichlorophenyl, 2,6-dichlorophenyl, 4-chloro-3-methylphenyl, 2,3,6-trichlorophenyl and 2,4,6-trichlorophenyl.

12. Use of a compound as defined in any one of claims 8 to 11 in the preparation of a compound of formula (I) as defined in any one of claims 1 to 6.

13. Use of a compound of formula (XVI):



(XVI)

wherein R^1 and R^2 are as defined in any one of claims 1 to 5,

in the preparation of a compound of formula (I) as defined in any one of claims 1 to 5 wherein R^3 is other than a methyl group.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 or pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or diluent.

15. A compound according to any one of claims 1 to 6 or a composition according to claim 14 for use in a method of treatment of the human or animal body by therapy.

16. Use of a compound according to any one of claims 1 to 6 or a composition according to claim 14 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 of colorectal cancer or neurodegenerative diseases.

17. A method for treating pain, fever or inflammation, inhibiting prostanoid-induced smooth muscle contraction or preventing colorectal cancer or neurodegenerative diseases which comprises administering to a human or animal subject in need of treatment an effective amount of a compound according to any one of claims 1 to 6 or a composition according to claim 14.

INTERNATIONAL SEARCH REPORT

inte onal Application No
PCT/EP 99/06873

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/38 C07D309/40 C07D405/04 C07D409/04 A61K31/35
C07C317/24 C07C311/29

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 C07C

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 14014 A (PARKE,DAVIS &CY.) 26 May 1995 (1995-05-26) claims; example 80	1,14-16
X	WO 96 06840 A (MERCK FROSST) 7 March 1996 (1996-03-07) page 37 -page 50; examples 1-11	8-11
X	US 3 901 908 A (K. FITZI) 26 August 1975 (1975-08-26) column 15 -column 21; example 12	8-11

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[X] Further documents are listed in the continuation of box C.

[X] 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	Date of mailing of the international search report
12 January 2000	01/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 99/06873

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document. with indication.where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 117, no. 74, 1992 Columbus, Ohio, US; abstract no. 202023e, page 719; XP002127319 abstract & JP 04 173391 A (SANYO) 22 June 1992 (1992-06-22) ---	8-11
X	CHEMICAL ABSTRACTS, vol. 84, no. 9, 1976 Columbus, Ohio, US; abstract no. 59566b, page 538; XP002127320 abstract & CZ 156 247 A (M. PROTIVA ET AL.) 15 December 1974 (1974-12-15) ---	8-11
X	V. VALENTA ET AL.: "ALPHA-(4-TOLYL)DOPAMINE DERIVATIVES" COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS., vol. 48, no. 5, 1983, pages 1447-1464, XP002127318 ACADEMIC PRESS, LONDON., GB ISSN: 0010-0765 page 1449 -page 1455; figure XV ---	8-11
X,P	WO 99 25697 A (KOWA CO) 27 May 1999 (1999-05-27) -& CHEMICAL ABSTRACTS, vol. 131, no. 1, 1999 Columbus, Ohio, US; abstract no. 05263, XP002127321 abstract * CAS RN 225668-35-9:ETHANONE,2-p-CHLOROPHENYL-1-(4 -METHYLTHIO-PHENYL)-* -----	8-11

1

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 99/06873

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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. [X] Claims Nos.: 17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 17 is 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 compound/composition.

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 II Observations where unity of invention is lacking (Continuation of item 2 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

Information on patent family members

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