CAVELIER / ...o- 13440-841-001-4

Industria y Comercio
SUPERINTENDENCIA

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SUPERINDUSTRIA Y COMERCIO ...ión
Radicacion : 02082841 00000000 Folios: 184
Fecha (AMD): 2002-09-16 16:39:53
Tramite : 011 PCT-PATENT 373 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1 **SOLICITUD DE:**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 **SOLICITANTE (71)**

Nombre: **ALMIRALL PRODESFARMA AG** sociedad constituida y existente bajo las leyes de la Suiza.

Dirección: Lindenhof,
Dorfstrasse 38
CH-6341 Baar
Suiza.

Domicilio: Baar, Suiza.

IDENTIFICACION

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual_____

Número: _____

3 **REPRESENTANTE O APODERADO**

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Teléfono: 347 36 11
Fax:: 217 92 11
E-mail: clientes@camyp.com.
Domicilio: Bogotá, Colombia.

IDENTIFICACION

C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual_____

Número: 438.019 T.P. 31.929

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C/Rosello 479, 3°,
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España.

5 **PCT (86)**

Solicitud Internacional No. PCT/EP01/03042 Fecha: 16 de marzo 2001
Publicación Internacional No. WO 01/68633 A1 Fecha : 20 de septiembre de 2001

6 **Título (54)** DERIVADOS DE 2-FENILPIRAN-4-ONA

7 **Clasificación Internacional (51)** C07D 309/040 , A61K 31/351

8 **Prioridad** SI ☒ NO ☐

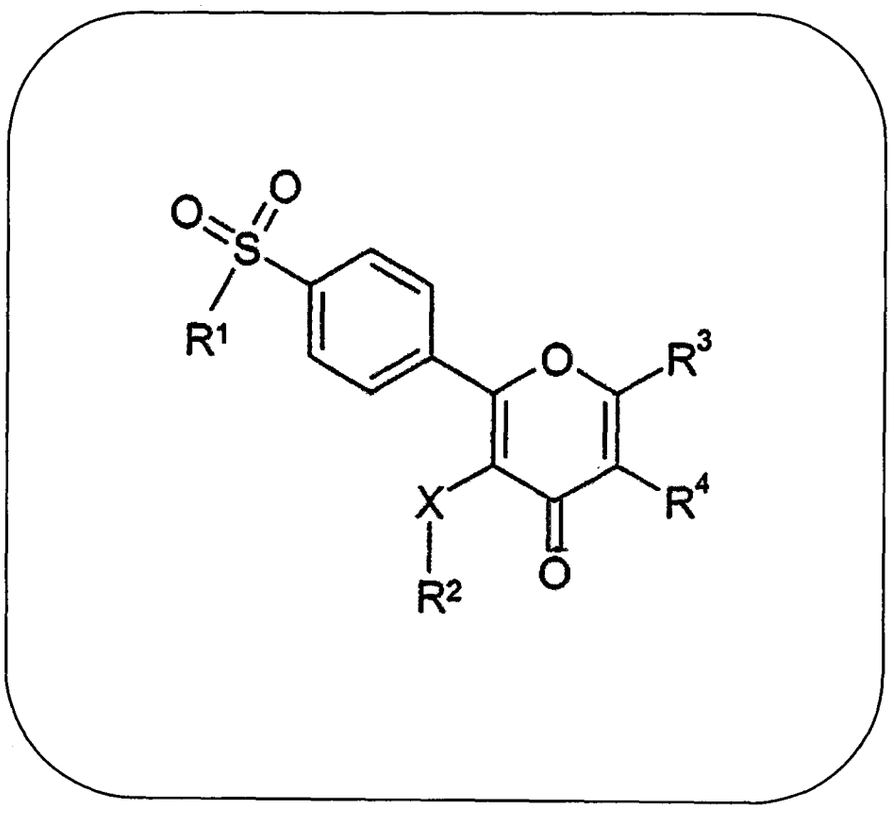
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
ES.	16 de marzo de 2000	200000637

9 **Comprobante de pago No.:** 02-56220 **Fecha:** 26 de agosto de 2002

10 **Anexos:**

- [x] Comprobante de pago de la tasa de presentación de la solicitud por 378.000.oo.
- [ ] Comprobante de pago por reivindicación de prioridad.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [x] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11 **FIGURA CARACTERISTICA:**



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68633 A1

(51) International Patent Classification[7]: C07D 309/40, 405/12, A61K 31/351, A61P 29/00, C07D 309/38

(21) International Application Number: PCT/EP01/03042

(22) International Filing Date: 16 March 2001 (16.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
200000637 16 March 2000 (16.03.2000) ES

(71) Applicant *(for all designated States except US)*: ALMIRALL PRODESFARMA S.A. [ES/ES]; General Mitre 151, E-08022 Barcelona (ES).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: CRESPO CRESPO, Maria Isabel [ES/ES]; Comte d'Urgell 259, 6° 3a, E-08036 Barcelona (ES). JIMENEZ MAYORGA, Juan Miguel [ES/ES]; Dr. Roux 74, Ppal. 2a, E-08017 Barcelona (ES). MATALLANA JULIA, Josep Lluis [ES/ES]; Via Europa 30, 7°, 2a, E-08304 Mataro (ES). FEIXAS GRAS, Joan [ES/ES]; C/Rosello 479, 3°, E-08025 Barcelona (ES).

(74) Agents: GOLDIN, Douglas, Michael et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

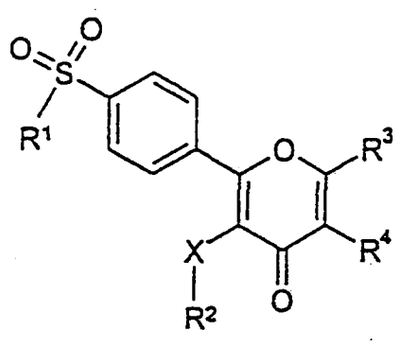
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 2-PHENYLPYRAN-4-ONE DERIVATIVES



(I)

(57) Abstract: The present invention relates to 2-(4-sulphonylphenyl)pyran-4-one derivatives of general formula (I), processes for their preparation, pharmaceutical compositions containing them, and their medical uses.

WO 01/68633 A1

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
N.81547 DMG		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 01/03042	16/03/2001	16/03/2000
Applicant		
ALMIRALL PRODESFARMA S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. =

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/03042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/40 C07D405/12 A61K31/351 A61P29/00 C07D309/38

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 14014 A (PARKE,DAVIS) 26 May 1995 (1995-05-26) claims; example 80	1,24
P,X	WO 00 18753 A (ALMIRALL PRODESFARMA) 6 April 2000 (2000-04-06) page 1 -page 33; claims 1-6,14-17	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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

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

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

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

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 July 2001	12/07/2001

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

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/03042

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

Although claim 27 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

International Application No
PCT/EP 01/03042

8

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9514014 A	26-05-1995	US 5808062 A	15-09-1998
		AU 695088 B	06-08-1998
		AU 4097497 A	08-01-1998
		AU 687465 B	26-02-1998
		AU 8091194 A	06-06-1995
		AU 682417 B	02-10-1997
		AU 8127694 A	06-06-1995
		BG 62770 B	31-07-2000
		BG 100564 A	31-12-1996
		CA 2174124 A	26-05-1995
		CA 2176044 A	26-05-1995
		CZ 9601343 A	14-08-1996
		EP 0729465 A	04-09-1996
		EP 0729466 A	04-09-1996
		FI 962019 A	20-05-1996
		FI 962020 A	31-05-1996
		HR 940938 A	30-06-1997
		HR 940939 A	30-06-1997
		HU 74888 A	28-02-1997
		HU 77719 A	28-07-1998
		JP 9505293 T	27-05-1997
		JP 9505295 T	27-05-1997
		MD 960171 A	30-09-1997
		NO 962015 A	15-05-1996
		NO 962016 A	15-05-1996
		NZ 275325 A	30-08-1999
		PL 314484 A	16-09-1996
		RU 2136674 C	10-09-1999
		SK 63996 A	06-11-1996
		WO 9514013 A	26-05-1995
		US 6005103 A	21-12-1999
		ZA 9409147 A	21-07-1995
		ZA 9409150 A	31-07-1995
WO 0018753 A	06-04-2000	ES 2154561 A	01-04-2001
		AU 6084799 A	17-04-2000
		BR 9913939 A	12-06-2001

9
9

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
N.81547		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP01/03042	16/03/2001	16/03/2000
International Patent Classification (IPC) or national classification and IPC C07D309/40		
Applicant ALMIRALL PRODESFARMA S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26/09/2001	06.03.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Friebel, F Telephone No. +49 89 2399 8552

Form PCT/IPEA/409 (cover sheet) (January 1994)

10

TERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/03042

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-58 as originally filed

Claims, No.:

1-27 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 27.

because:

☒ the said international application, or the said claims Nos. 27 - IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-27
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-26

point III:

Claim 27 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

point V:

Subject-matter of the present application are 2-phenylpyran-4-one derivatives which are selective COX-2 inhibitors.
The structural characteristics are - in addition to the sulfonated phenyl nucleus at the 2-position - the radical R^2 linked via the bridging member -X- to C-3 of the pyrane core structure. Such compounds are not disclose in the available prior art; novelty is therefore acknowledged; Art.33(2).
Furthermore, such compounds are also not made obvious by the pyrone derivatives of WO 95/14014, not to mention that these prior art compounds show a different activity, viz. protease inhibitiors and antiviral agents (Art.33(3) PCT).

As concersn the P-Dokument WO 00/18753, for the sake of completeness the Applicant is already now informed that when entering into the reg. phase before the EPO present Claim 1 should be deleted.

For the assessment of the present claim 27 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

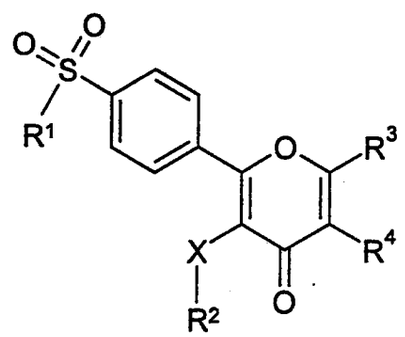
2-PHENYLPYRAN-4-ONE DERIVATIVES

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 $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkyl, hydroxymethyl, alkoxymethyl, alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or

difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents a hydrogen atom, or an alkyl, alkenyl or alkynyl group or a halogen atom; and

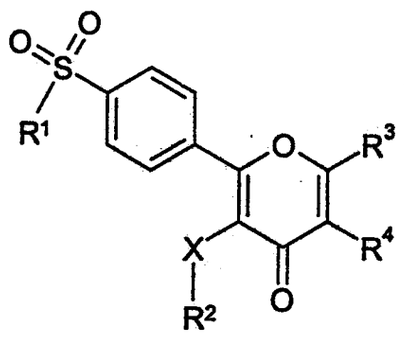
X represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

In the compounds of formula (I), when R^3 is an alkenyloxymethyl group, it is typically an alkenylmethoxymethyl group.

In a preferred embodiment the invention provides a compound of formula (I):

(I)



wherein:

R^1 represents an alkyl or -NR^5R^6 group, wherein R^5 and R^6 each independently represent 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 an alkyl, hydroxymethyl, alkoxymethyl, alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents a hydrogen atom, or an alkyl, alkenyl or alkynyl group or a halogen atom; and

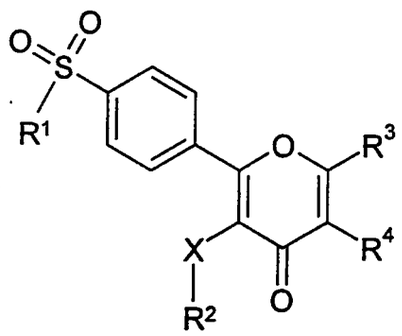
X represents a single bond, an oxygen atom, a sulfur atom or a methylene group; with the proviso that when R^4 is a hydrogen atom R^3 is an alkenylmethoxymethyl, C_3-C_7 cycloalkylmethoxymethyl or R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

or a pharmaceutically acceptable salt thereof.

In this preferred embodiment, when R^3 is an alkenyloxymethyl group, it is typically an alkenylmethoxymethyl group.

In another preferred embodiment the invention provides a compound of formula (I):

(I)



wherein:

R^1 represents an alkyl or $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkyl, hydroxymethyl, alkoxymethyl, alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents an alkyl, alkenyl or alkynyl group or a halogen atom; and

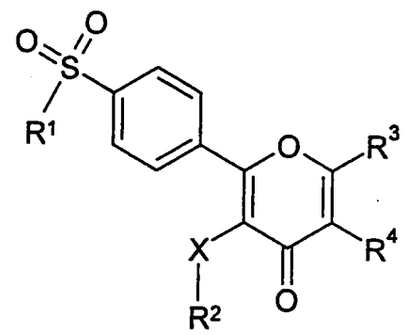
X represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

In this further preferred embodiment, when R^3 is an alkenyloxymethyl group, it is typically an alkenylmethoxymethyl group.

In another preferred embodiment the invention provides a compound of formula (I):

(I)



wherein:

R^1 represents an alkyl or $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkenyloxymethyl or C_3-C_7 cycloalkylmethoxymethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents a hydrogen atom; and

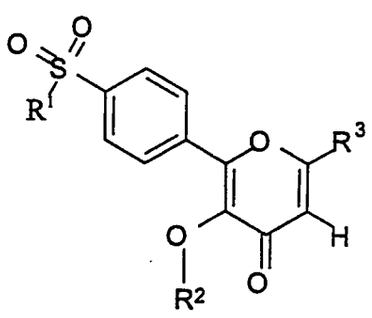
X represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

In this further preferred embodiment, when R^3 is an alkenyloxymethyl group, it is typically an alkenylmethoxymethyl group.

In another preferred embodiment the invention provides a compound of formula (IA):

(IA)



wherein:

R^1 represents a methyl or ethyl group;

R^2 represents a phenyl group which may be unsubstituted or substituted by one or more substituents selected from halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

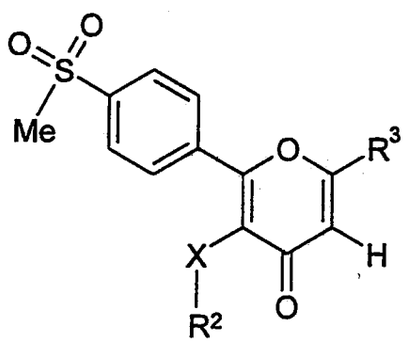
R^3 represents an alkyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group;

provided that when R^3 is methyl, R^2 is either (a) a phenyl group having at least one substituent selected from trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups, (b) a monosubstituted phenyl group having a halogen atom or an alkyl group at the 3-position or having a bromine atom or an alkyl group at the 2-position 1 or (c) a phenyl group having two or more substituents wherein at least one substituent is a bromine atom or wherein an alkyl group is present at the 2- or 4-position, or (d) 3-methyl-4-fluoro-phenyl;

or a pharmaceutically acceptable salt thereof.

In the compounds of formula (IA), R^1 is typically a methyl group. Further, when R^3 is a methyl group, R^2 is typically phenyl having at least one substituent selected from trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups; with the substituent preferably being selected from hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups.

The invention also provides a compound of formula (IB):



(IB)

wherein:

R^2 represents 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 an alkyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group;

or a pharmaceutically acceptable salt thereof.

In the formulae (IA) and (IB), R^3 is typically a hydroxymethyl, methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, difluoromethyl, hydroxycarbonyl, cyclopropoxymethyl or cyclobutoxymethyl group.

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^7 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. 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 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, alkyl groups, preferably methyl groups, and/or alkoxy groups, preferably methoxy groups. Halogen atoms are preferably selected from fluorine, chlorine or bromine atoms.

R^2 is preferably a phenyl group that is unsubstituted or has 1, 2 or 3 substituents, more preferably 1 or 2 substituents. Preferably the substituents are independently seclected from methyl groups and chlorine, bromine and fluorine atoms. When R^2 is a phenyl group substituted by one or more halogens atoms and/or alkyl groups, preferably one of the substitutions is at the 2- or 3-position of the phenyl group.

In one preferred group of compounds R^2 is an unsubstituted phenyl group or a phenyl group substituted by a single halogen atom selected from fluorine, chlorine or bromine, a single methyl group or two halogen atoms which are the same or different and are selected from fluorine, chlorine or bromine.

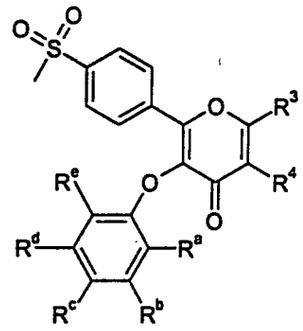
It is preferred that R^1 independently represents an unsubstituted alkyl group such as methyl, ethyl, propyl or butyl, preferably methyl or an NH_2 group (i.e. R^5 and R^6 in the above formula both independently represent an H atom).

It is also preferred that R^3 independently represents an unsubstituted C_{1-3} alkyl group such as methyl, ethyl or n-propyl or i-propyl, a nitrile group, a hydroxymethyl group, a methoxymethyl group, an ethoxymethyl group, a propoxymethyl group, an isopropoxymethyl group, a difluoromethyl group, a propenyloxymethyl group, a hydroxycarbonyl group, a cyclopropoxymethyl group, a cyclobutoxymethyl group, a cyclopropylmethoxymethyl group, a cyclobutylmethyloxymethyl group or a CH_3-COO-CH_2- group.

It is preferred that R^4 represents an alkyl group such as methyl or ethyl, an alkenyl group such as vinyl, an alkynyl group such as ethynyl, a halogen atom such as a chlorine or bromine atom or a hydrogen atom.

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

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



R^3	R^4	R^a	R^b	R^c	R^d	R^e
Me	H	H	Br	H	H	H
Me	H	Br	H	H	H	H
Me	H	H	Me	H	H	H
Me	H	Me	H	H	H	H
Me	H	Me	H	F	H	H
Me	H	Me	H	Cl	H	H
Me	H	F	H	Me	H	H
Me	H	Cl	H	Me	H	H
Me	H	H	Me	F	H	H
Me	H	H	F	Me	H	H
Me	H	H	Cl	Me	H	H
Me	H	F	H	Br	H	H
Me	H	Cl	H	Br	H	H
Me	H	Br	H	Br	H	H
Me	Cl	H	H	H	H	H
Me	Cl	H	H	F	H	H
Me	Cl	H	F	H	H	H
Me	Cl	F	H	H	H	H
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Me	Cl	Cl	H	H	H	H
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Me	Cl	F	H	H	F	H

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Me	Br	H	F	F	H	H
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Me	Br	H	Me	F	H	H
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Me	Me	Me	H	H	H	H
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Me	Me	F	H	Br	H	H
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Me	Me	H	F	Cl	H	H
Me	Me	F	H	Me	H	H
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Me	Me	Me	H	F	H	H
Me	Me	Me	H	Cl	H	H
Me	Me	H	Me	F	H	H
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CH_2OH	H	F	H	Br	H	H
CH_2OH	H	Br	H	F	H	H
CH_2OH	H	H	Cl	F	H	H
CH_2OH	H	H	F	Cl	H	H
CH_2OH	H	F	H	Me	H	H
CH_2OH	H	Cl	H	Me	H	H

CH_2OH	H	Me	H	F	H	H
CH_2OH	H	Me	H	Cl	H	H
CH_2OH	H	H	Me	F	H	H
CH_2OH	H	H	Me	Cl	H	H
CH_2OH	H	H	F	Me	H	H
CH_2OH	H	H	Cl	Me	H	H
CH_2OCH_3	H	H	H	H	H	H
CH_2OCH_3	H	H	H	F	H	H
CH_2OCH_3	H	H	F	H	H	H
CH_2OCH_3	H	F	H	H	H	H
CH_2OCH_3	H	H	H	Cl	H	H
CH_2OCH_3	H	H	Cl	H	H	H
CH_2OCH_3	H	Cl	H	H	H	H
CH_2OCH_3	H	H	H	Br	H	H
CH_2OCH_3	H	H	Br	H	H	H
CH_2OCH_3	H	Br	H	H	H	H
CH_2OCH_3	H	H	H	Me	H	H
CH_2OCH_3	H	H	Me	H	H	H
CH_2OCH_3	H	Me	H	H	H	H
CH_2OCH_3	H	F	H	F	H	H
CH_2OCH_3	H	F	H	H	F	H
CH_2OCH_3	H	H	F	F	H	H
CH_2OCH_3	H	F	H	H	H	F
CH_2OCH_3	H	Cl	H	Cl	H	H
CH_2OCH_3	H	Cl	H	H	Cl	H
CH_2OCH_3	H	H	Cl	Cl	H	H
CH_2OCH_3	H	Cl	H	H	H	Cl
CH_2OCH_3	H	F	H	Cl	H	H
CH_2OCH_3	H	Cl	H	F	H	H
CH_2OCH_3	H	F	H	Br	H	H
CH_2OCH_3	H	Br	H	F	H	H
CH_2OCH_3	H	H	Cl	F	H	H
CH_2OCH_3	H	H	F	Cl	H	H
CH_2OCH_3	H	F	H	Me	H	H
CH_2OCH_3	H	Cl	H	Me	H	H
CH_2OCH_3	H	Me	H	F	H	H
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CH_2OCH_3	H	H	Me	F	H	H
CH_2OCH_3	H	H	Me	Cl	H	H
CH_2OCH_3	H	H	F	Me	H	H
CH_2OCH_3	H	H	Cl	Me	H	H
CF_2H	H	H	H	H	H	H

CF_2H	H	H	H	F	H	H
CF_2H	H	H	F	H	H	H
CF_2H	H	F	H	H	H	H
CF_2H	H	H	H	Cl	H	H
CF_2H	H	H	Cl	H	H	H
CF_2H	H	Cl	H	H	H	H
CF_2H	H	H	H	Br	H	H
CF_2H	H	H	Br	H	H	H
CF_2H	H	Br	H	H	H	H
CF_2H	H	H	H	Me	H	H
CF_2H	H	H	Me	H	H	H
CF_2H	H	Me	H	H	H	H
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CF_2H	H	Cl	H	Cl	H	H
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CF_2H	H	Cl	H	H	H	Cl
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CF_2H	Me	F	H	F	H	H
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$CH_2OCH_2CH_3$	H	F	H	F	H	H
$CH_2OCH_2CH_2CH_3$	H	H	H	F	H	H
$CH_2OCH_2CH_2CH_3$	H	H	H	Cl	H	H
$CH_2OCH_2CH_2CH_3$	H	F	H	F	H	H

$CH_2OCH(CH_3)_2$	H	H	H	F	H	H
$CH_2OCH(CH_3)_2$	H	H	H	Cl	H	H
$CH_2OCH(CH_3)_2$	H	F	H	F	H	H
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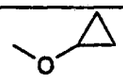
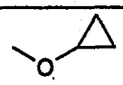
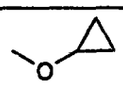
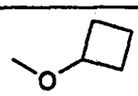
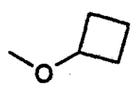
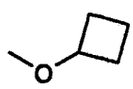
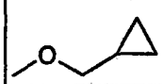
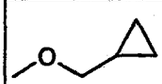
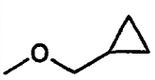
$CH_2OCH_2CH=CH_2$	H	H	H	Cl	H	H
$CH_2OCH_2CH=CH_2$	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H
	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H
	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H
	H	F	H	F	H	H
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CH_2OCOCH_3	H	F	H	H	H	H
CH_2OCOCH_3	H	H	H	Cl	H	H
CH_2OCOCH_3	H	H	Cl	H	H	H
CH_2OCOCH_3	H	Cl	H	H	H	H
CH_2OCOCH_3	H	H	H	Br	H	H
CH_2OCOCH_3	H	H	Br	H	H	H
CH_2OCOCH_3	H	Br	H	H	H	H
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CH_2OCOCH_3	H	H	F	F	H	H
CH_2OCOCH_3	H	F	H	H	H	F

CH_2OCOCH_3	H	Cl	H	Cl	H	H
CH_2OCOCH_3	H	Cl	H	H	Cl	H
CH_2OCOCH_3	H	H	Cl	Cl	H	H
CH_2OCOCH_3	H	Cl	H	H	H	Cl
CH_2OCOCH_3	H	F	H	Cl	H	H
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CH_2OCOCH_3	H	F	H	Br	H	H
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CH_2OCOCH_3	H	Me	H	F	H	H
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COOH	H	H	H	H	H	H
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COOH	H	F	H	H	H	H
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COOH	H	H	Cl	Cl	H	H
COOH	H	Cl	H	H	H	Cl
COOH	H	F	H	Cl	H	H
COOH	H	Cl	H	F	H	H
COOH	H	F	H	Br	H	H
COOH	H	Br	H	F	H	H
COOH	H	H	Cl	F	H	H
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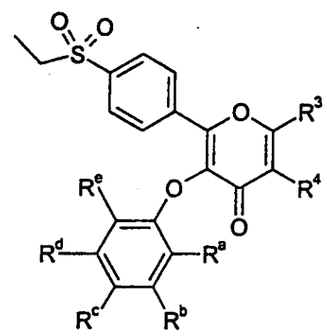
COOH	H	Me	H	F	H	H
COOH	H	Me	H	Cl	H	H



R^3	R^4	R^a	R^b	R^c	R^d	R^e
Me	H	F	H	F	H	H

and pharmaceutically acceptable salts thereof.

Of outstanding interest are:

3-(4-fluoro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;

3-(4-chloro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;

3-(2-chloro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;

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

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

3-(4-bromo-2-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran -4-one;

3-(4-bromo-2-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran -4-one;

3-(2,4-dibromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one;

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

2-(4-methanesulfonylphenyl)-6-methyl-3-(2-methylphenoxy)pyran-4-one;

2-(4-methanesulfonylphenyl)-6-methyl-3-(3-methylphenoxy)pyran-4-one;

3-(2-fluoro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;

3-(2,4-difluorophenoxy)-6-ethyl-2-(4-methanesulfonylphenyl)-5-methyl pyran-4-one;

3-chloro-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;

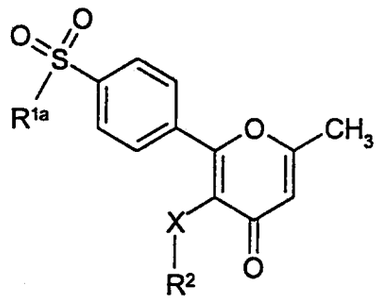
3-chloro-5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl

pyran-4-one;
3-chloro-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-bromo-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-bromo-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methylpyran-4-one;
3-(2,4-difluorophenoxy)-5,6-dimethyl-2-(4-methanesulfonylphenyl) pyran-4-one;
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl-5-vinyl pyran-4-one;
3-(2,4-difluorophenoxy)-5-ethyl-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-(2,4-difluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl) pyran-4-one;
3-(4-fluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one;
3-(4-chlorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one;
3-(2-fluoro-4-bromophenoxy)-6-hydroxymethyl-2-(4-methanesulfonyl phenyl)pyran-4-one;
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethyl pyran-4-one;
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one;
3-(4-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one;
acetic acid [5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
acetic acid [5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
acetic acid [5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid;
5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid;
6-(1,1-difluoromethyl)-3-(2,4-difluorophenoxy)-2-(4-methanesulfonyl phenyl)pyran-4-one;

6-(1,1-difluoromethyl)-3-(4-bromophenoxy)-2-(4-methanesulfonyl phenyl)pyran-4-one;
6-(1,1-difluoromethyl)-2-(4-methanesulfonylphenyl)-3-(4-methyl phenoxy)pyran-4-one;
3-bromo-2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)pyran-4-one;
2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methane-sulfonylphenyl)-3-methylpyran-4-one;
and pharmaceutically acceptable salts thereof.

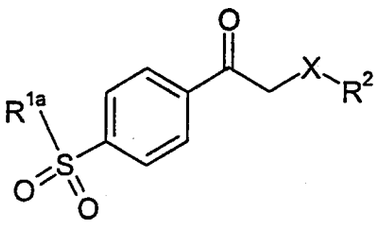
The present invention also provides processes for preparing a compound of formula (I) which depend on the definition of R^3 and R^4. When R^3 is an alkyl group and R^4 is a hydrogen atom or an alkyl group, compounds of formula (I) are prepared according to the definition of R^1. Thus, compounds of formula (I) in which R^3 is a methyl group, R^4 is a hydrogen atom and R^1 is an alkyl or $-NR^5R^6$ group in which R^5 and R^6 are alkyl groups, viz. a 2-phenylpyran-4-one derivative of formula (II):

(II)



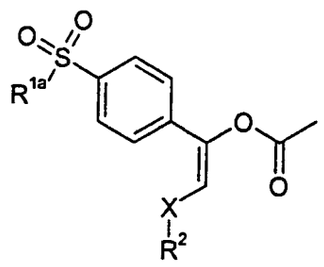
wherein R^{1a} is an alkyl or $-NR^{5a}R^{6a}$ group in which R^{5a} and R^{6a} are each independently alkyl groups, and R^2 and X are as defined above, which comprises reacting a carbonyl derivative of formula (III):

(III)



wherein R^{1a}, R^2 and X are as defined above with an excess of anhydrous acetic acid or acetic anhydride and polyphosphoric acid, at a temperature from 90°C to 150°C.

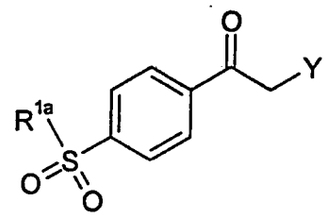
The compound of formula (II) may also be prepared by reacting a vinyl derivative of formula (IV):

(IV) 

wherein R^{1a}, R^2 and X are as defined above, with an excess of acetic anhydride and polyphosphoric acid at a temperature from 80°C to 120°C.

The vinyl derivative of formula (IV) may be obtained by reacting a carbonyl derivative of formula (III) with acetic anhydride and methanesulfonic acid at a temperature from 50°C to 100°C.

The carbonyl derivative of formula (III) may be obtained by methods well known in the literature (EP-A-714883; WO 96/06840; WO 96/31509 and DE-2064520) or when X represents an oxygen or sulfur atom, by reacting a phenacyl derivative of formula (V):

(V) 

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

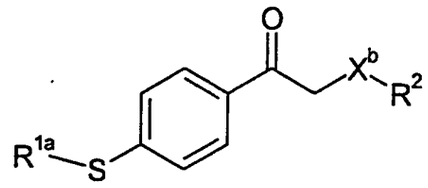
(VI) $HX^a - R^2$

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

The reaction between the phenacyl derivative of formula (V) and the alcohol or thiol of formula (VI) 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 such 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 (VII):

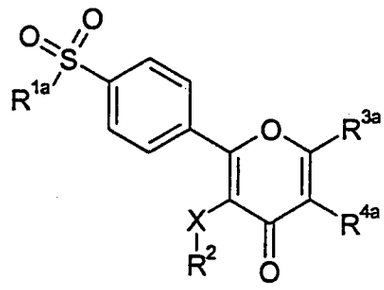
(VII)



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 from 10°C to 40°C.

The present invention also provides a process for the preparation of compound of formula (I) wherein R^3 and R^4 are alkyl groups and R^1 is an alkyl or $-NR^5R^6$ group in which R^5 and R^6 are alkyl group, viz. 2-phenylpyran-4-one derivative of formula (VIII):

(VIII)



wherein R^{4a} is an alkyl group, R^{3a} represents a CH_2-R^{4a} group and R^{1a}, R^2 and X are as defined above, which comprises reacting a carbonyl derivative of formula (III) with an excess of an anhydride of formula (IX):

(IX) $(R^{4a}CH_2CO)_2O$

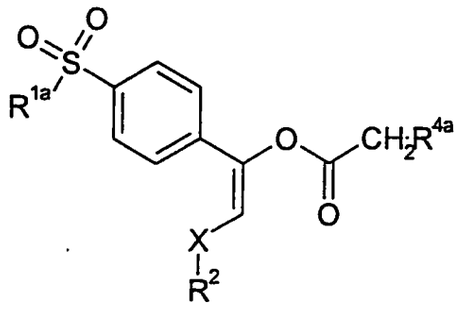
or a carboxylic acid of formula (X):

(X) $R^{4a}CH_2COOH$

and polyphosphoric acid at a temperature from 90°C to 150°C.

The compound of formula (VIII) can also be obtained by reacting a vinyl derivative of formula (XI):

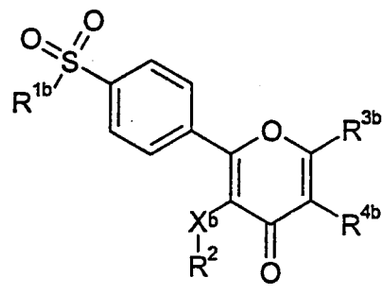
(XI)



wherein R^{1a}, R^2, R^{4a} and X are as defined above with an excess of an anhydride of formula (IX) and polyphosphoric acid at a temperature from 90°C to 150°C. The vinyl derivative of formula (XI) may be prepared by reacting a carbonyl derivative of formula (III) with an anhydride of formula (IX) and methanesulfonic acid at a temperature from 50°C to 100°C.

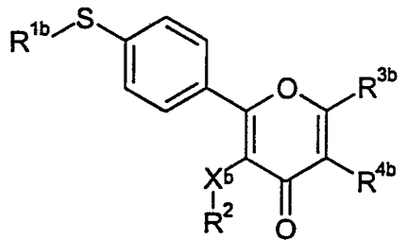
The present invention also provides a process for the preparation of a compound of formula (I) wherein R^3 is a alkyl group, R^4 is a hydrogen atom, or an alkyl group, R^1 is an alkyl group, and X is other than a sulfur atom viz. 2-phenylpyran-4-one derivative of formula (XII):

(XII)



wherein R^{1b} is an alkyl group, R^{3b} is a methyl group or a $R^{4b}CH_2$ group, R^{4b} is a hydrogen atom or an alkyl group and R^2 and X^b are as defined above by reacting a mercapto derivative of formula (XIII):

(XIII)

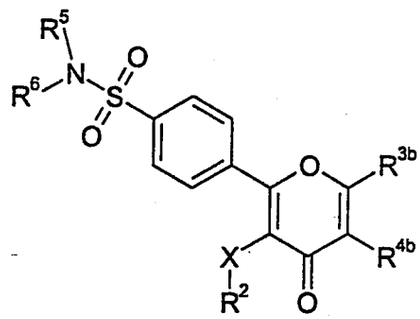


wherein R^{1b}, R^{3b}, R^{4b}, R^2 and X^b are as defined above with an oxidizing agent, preferably with magnesium monoperoxyphthalate or 3-chloroperoxybenzoic acid.

The reaction between the mercapto derivative of formula (XIII) and the oxidizing agent is preferably carried out, as previously disclosed for the compound of formula (VII), 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.

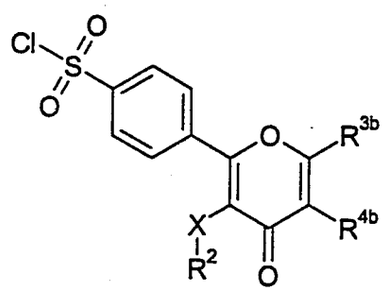
The present invention additionally provides a process for the preparation of a compound of formula (I) wherein R^1 is a $-NR^5R^6$ group, R^3 is an alkyl group and R^4 is a hydrogen atom, or an alkyl group viz. 2-phenylpyran-4-one derivative of formula (XIV):

(XIV)



wherein R^2, R^{3b}, R^{4b}, R^5, R^6 and X are as defined above by reacting a chlorosulfonyl derivative of formula (XV):

(XV)



wherein R^2, R^{3b}, R^{4b} and X are as defined above with an amine of formula (XVI):

(XVI) R^5-NH-R^6

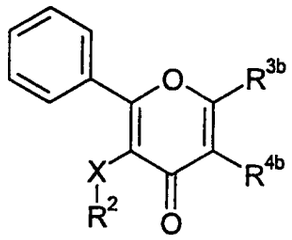
wherein R^5 and R^6 are as defined above.

This reaction is preferably carried out at a temperature of from

10°C to 40°C.

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

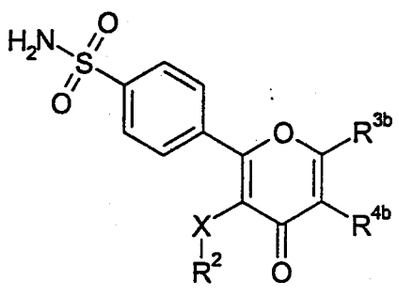
(XVII)



wherein R^2, R^{3b}, R^{4b} and X are as defined above with chlorosulfonic acid, preferably at a temperature of from 80°C to 120°C.

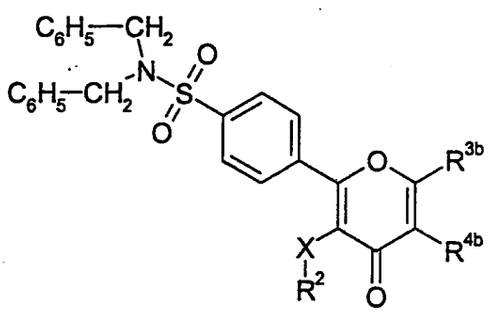
The present invention further provides a process for the preparation of a compound of formula (I) wherein R^3 is an alkyl group, R^4 is an hydrogen atom or an alkyl group and R^1 is a $-NR^5R^6$ group wherein R^5 and R^6 are hydrogen, viz, the 2-phenylpyran-4-one derivative of formula (XVIII):

(XVIII)



wherein R^2, R^{3b}, R^{4b} and X are as defined above by debenzylation of the corresponding N,N-dibenzyl derivative of formula (XIX):

(XIX)



wherein R^2, R^{3b}, R^{4b} and X are as defined above.

The debenzylation is preferably carried out with an excess of

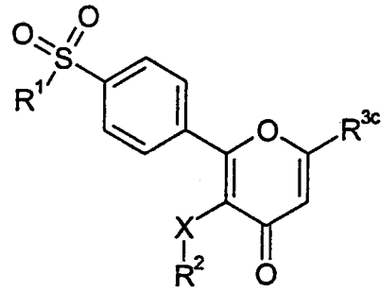
trifluoroacetic, sulfuric or methanesulfonic acid at a temperature of from 0°C to 120°C.

The intermediate of formula (XIX) may be prepared according to the above processes using appropriate starting materials wherein R^5 and R^6 (or R^{5a} and R^{6a}) both represent benzyl groups.

The intermediate of formula (V) and (VII) 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 96/06840.

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

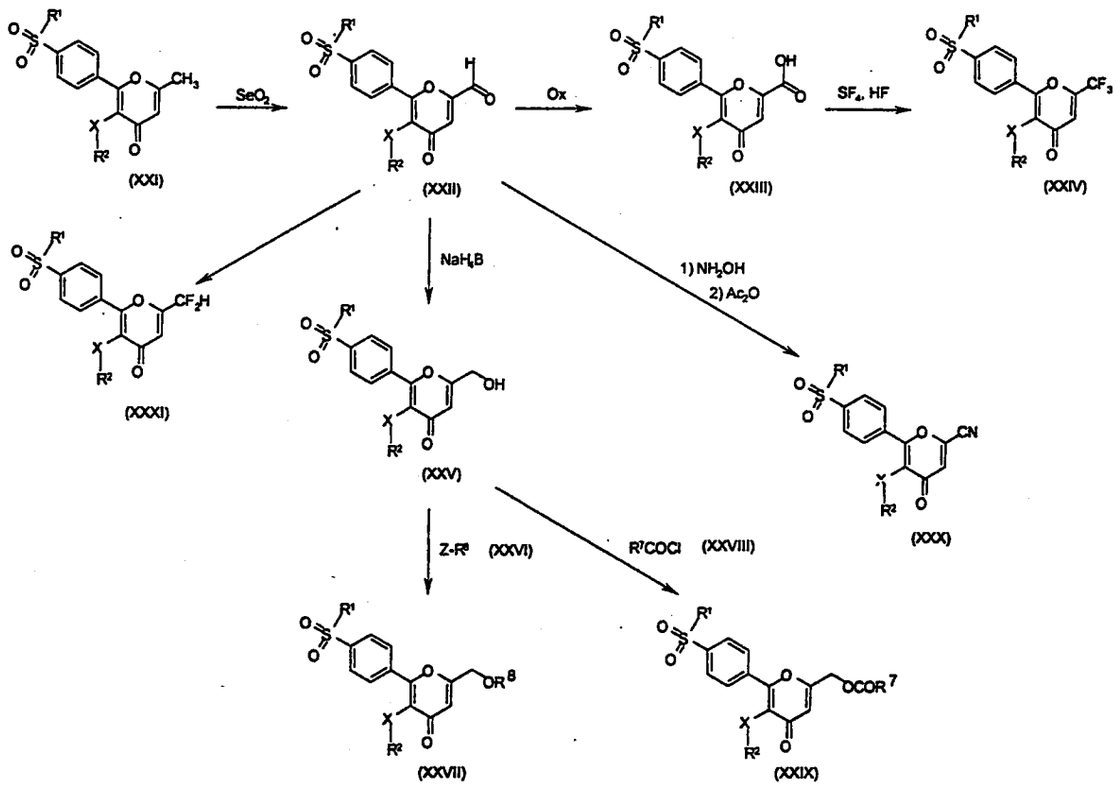
The 2-phenylpyran-4-one derivatives of formula (I) wherein R^3 is other than an alkyl group and R^4 is a hydrogen atom, viz. 2-phenylpyran-4-one derivatives of formula (XX):



(XX)

wherein R^{3c} is a hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, alkenylmethoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxy methyl, hydroxycarbonyl, nitrile, trifluoromethyl, difluoromethyl group, or a CH_2OCOR^7 group, wherein R^7 is an alkyl or a phenyl group, and R^1, X and R^2 are as defined above, can be prepared by processes which are

represented in the following scheme:



As it can be seen in the scheme, 2-phenylpyran-4-one derivatives of general formula (XX), are prepared from compounds of formula (I) in which R^3 is a methyl group and R^4 is a hydrogen atom, viz. compound of formula (XXI), which processes of preparation have been disclosed above. In a first stage, compounds of formula (XXI) 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 (XXII) is obtained, which is used as starting material to obtain the compounds of general formula (XX).

The compounds of formula (XX) wherein R^{3c} is a hydroxycarbonyl group, viz. compound of formula (XXIII), are prepared from the corresponding aldehyde (XXII) by reaction with an oxidizing agent as pyridinium dichromate or chromium (IV) oxide in an organic solvent such as N,N-dimethylformamide, ethanol or acetone/sulfuric acid, at a temperature between -5°C and 35°C. The obtained compounds (XXIII) are used as starting materials to obtain compounds of formula (I) wherein R^{3c} is a trifluoromethyl group, viz. compound of formula (XXIV). The

reaction is carried out by reaction of compounds (XXIII) with a mixture of sulphur tetrafluoride and hydrogen fluoride, optionally in the presence of an organic solvent such as methylene chloride, in a pressure vessel, and at a temperature from 20°C to 140°C.

The compounds of formula (XX) wherein R^{3c} represents a hydroxymethyl group, viz. compounds of formula (XXV) are prepared by reduction of compounds of formula (XXII) 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 of formula (XXV) with an appropriate halide of formula (XXVI):

(XXVI) $Z - R^8$

wherein Z represents a chlorine, bromine or iodine atom and R^8 represents an alkyl, C_3-C_7 cycloalkyl, alkenylmethyl, C_3-C_7 cycloalkylmethyl, or benzyl group, provide the compounds of formula (XX) wherein R^{3c} is an alkoxymethyl, C_3-C_7 cycloalkoxymethyl, alkenylmethoxymethyl, C_3-C_7 cycloalkylmethoxymethyl or benzyloxymethyl group, viz. compounds of formula (XXVII). The reaction is carried out in an organic solvent 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.

Further more, the reaction of compounds of formula (XXV) with an appropriate acyl halide of formula (XXVIII):

(XXVIII) R^7COCl

wherein R^7 represents an alkyl or a phenyl group provide compounds of formula (XXIX). The reaction is carried out in an organic solvent such as tetrahydrofuran, methylene chloride, chloroform or dioxane in the presence of a tertiary amine, such as triethylamine, at a temperature from 20°C to the boiling point of the solvent.

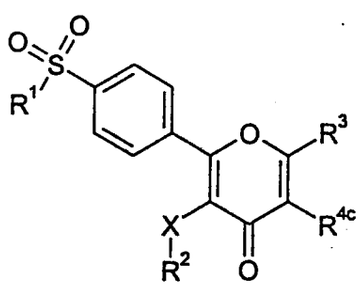
Also aldehydes of formula (XXII) are used as starting material to obtain compounds of formula (XX) wherein R^{3c} is a nitrile group, viz. compounds of formula (XXX). The reaction is carried out in a first stage by treatment of aldehydes (XXII) with hydroxylamine hydrochloride and formic acid at a temperature 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 (XX) wherein R^{3c} represents a difluoromethyl group, viz. compounds of formula (XXXI), are prepared from aldehydes of formula (XXII) 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 such as methylene chloride, benzene or toluene and at a temperature from 0°C to 130°C.

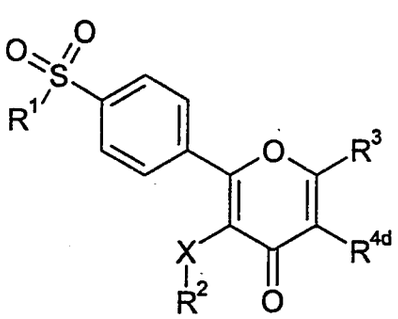
The present invention also provides a process for the preparation of compound of formula (I) wherein R^4 is other than a hydrogen atom, viz. 2-phenylpyran-4-one derivative of formula (XXXII):

(XXXII)



wherein R^{4c} is an alkyl, alkenyl or alkynyl group and R^1, R^2, R^3 and X are as defined above, which comprises reacting a compound of formula (XXXIII):

(XXXIII)



wherein R^{4d} is a chlorine, bromine or iodine atom, preferably a bromine atom and R^1, R^2, R^3 and X are as defined above, with a tin derivative of formula (XXXIV):

(XXXIV) $R^{4c}\ Sn\ (R^9)_3$

wherein R^{4c} is as defined above and R^9 is an alkyl group. The reaction is carried out in a solvent such as dimethylformamide, tetrahydrofuran or dioxane, in the presence of a tertiary amine, such as triethylamine,

with tri-o-tolylphosphine and palladium (II) acetate, and at a temperature from 20°C to 150°C.

The derivative of formula (XXXIII), wherein R^{4d} is preferably a bromine atom, may be obtained by reacting a derivative of formula (XX) or a derivative of formula (XXI) with bromine or pyridinium tribromide, in an organic solvent such as 1,1,2,2-tetrachloroethane, methylene chloride or chloroform, in a pressure vassel, and at a temperature from 20°C to 180°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 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.

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.

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

TABLE 1: COX-1 and COX-2 Inhibition

Example	COX-1 IC_{50} (µM)	COX-2 IC_{50} (µM)	Ratio COX-1/COX-2
1	21.2	0.18	118
2	38.5	0.13	296
3	16.3	0.24	68
6	40.2	0.15	268
7	33.4	0.21	159
8	57.5	1.13	51
10	19.9	0.086	231
11	14.2	0.30	47
16	26.0	0.53	74
17	20.0	0.78	27
18	76.7	0.82	93
19	14.6	0.082	178
20	31.2	1.43	22
21	35.6	0.58	62
22	53.0	0.19	279
23	2% at 100 µM	1.44	>70
24	13% at 100 µM	0.60	>150
26	21.1	0.17	124
27	86.3	0.32	270
28	91.9	0.44	209
30	50.3	0.14	359
31	17% at 100 µM	1.10	>90
32	450	0.42	1070
36	28.5	0.097	294

Indomethacin	0.19	0.22	0.86

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

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. 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 60, 100 or 200.

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 disease.

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.

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 or treatment of colorectal cancer or neurodegenerative diseases, for example, Alzheimer disease.

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 and myocardial ischaemia.

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

Accordingly, the 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 that 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 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.

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 Preparation and Examples, which do not limit the scope of the invention in any way.

PREPARATION 1

2-(2,4-Difluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone

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, 76%) as an off-white solid.

b) A solution of 80% magnesium monoperoxyphthalate hexahydrate (15.26 g; 25 mmol) in water (20 ml) was added to a solution of the above compound (6.60 g; 22 mmol) in methylene chloride (100 ml). 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, 89%) as an off-white solid.

δ (DMSO): 3.31 (s, 3H), 5.72 (s, 2H), 6.93-7.05 (m, 1H), 7.15-7.36 (m, 2H), 8.12 (d, J=8.5 Hz, 2H), 8.22 (d, J=8.5 Hz, 2H).

PREPARATION 2

2-(4-Fluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (72% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-fluorophenol by the procedure described in Preparation 1.

δ (DMSO): 3.32 (s, 3H), 5.62 (s, 2H), 7.01-7.04 (m, 2H), 7.05-7.17 (m, 2H), 8.13 (d, J=8.0 Hz, 2H), 8.25 (d, J=8.0 Hz, 2H).

PREPARATION 3

2-(4-Chlorophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (89% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-chlorophenol by the procedure described in Preparation 1.

δ (DMSO): 3.30 (s, 3H), 5.65 (s, 2H), 7.03 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 8.12 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.5 Hz, 2H).

PREPARATION 4

2-(4-Fluoro-2-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (75% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-fluoro-2-methylphenol by the procedure described in Preparation 1.

δ (DMSO): 2.22 (s, 3H), 3.30 (s, 3H), 5.63 (s, 2H), 6.89-7.06 (m, 3H), 8.08 (d, J=8.0 Hz, 2H), 8.21 (d, J=8.0 Hz, 2H)

PREPARATION 5

2-(4-Chloro-2-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (77% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-chloro-2-methylphenol by the procedure described in Preparation 1.

δ (DMSO): 2.23 (s, 3H), 3.31 (s, 3H), 5.68 (s, 2H), 6.96 (d, J=8.5 Hz, 1H), 7.15 (d, J=8.5 Hz, 1H), 7.25 (s, 1H), 8.12 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.5 Hz, 2H).

PREPARATION 6

2-(2-Chloro-4-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (84% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 2-chloro-4-methylphenol by the procedure described in Preparation 1.

δ (DMSO): 2.23 (s, 1H), 3.32 (s, 3H), 5.74 (s, 2H), 7.02-7.04 (m, 2H), 7.24 (s, H), 8.12 (d, J=8.1 Hz, 2H), 8.22 (d, J=8.1 Hz, 2H).

PREPARATION 7

2-(2-Bromophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (72% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 2-bromophenol by the procedure described in Preparation 1.

δ ($CDCl_3$): 3.07 (s, 3H), 5.30 (s, 2H), 6.80-6.94 (m, 2H), 7.20-7.26 (m, 1H), 7.53 (d, J=7.5 Hz, 1H), 8.08 (d, J=9.0 Hz, 2H), 8.23 (d, J=9.0 Hz, 2H).

PREPARATION 8

2-(3-Bromophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (57% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 3-bromophenol by the procedure described in Preparation 1.

δ (DMSO): 3.33 (s, 3H), 5.72 (s, 2H), 7.03-7.06 (m, 1H), 7.17 (d, J=8.0 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.32 (s, 1H), 8.13 (d, J=8.0 Hz, 2H), 8.24 (d, J=8.0 Hz, 2H).

PREPARATION 9

2-(4-Bromophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (81% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-bromophenol by the procedure described in Preparation 1.

δ ($CDCl_3$): 3.33 (s, 3H), 5.66 (s, 2H), 7.00(d, J=9.0 Hz, 2H), 7.46 (d, J=9.0 Hz, 2H), 8.12 (d, J=9.0 Hz, 2H), 8.24 (d, J=9.0 Hz, 2H).

PREPARATION 10

2-(4-Bromo-2-fluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (78% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-bromo-2-fluorophenol by the procedure described in Preparation 1.

δ (DMSO): 3.32 (s, 3H), 5.80 (s, 2H), 7.10 (t, J=7.5 Hz, 1H), 7.37 (t, J=7.5 Hz, 1H), 7.60 (d, J=7.5 Hz, 1H), 8.13 (d, J=9.0 Hz, 2H), 8.24 (d, J=9.0 Hz, 2H).

PREPARATION 11

2-(4-Bromo-2-chlorophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (68% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 4-bromo-2-chlorophenol by the procedure described in Preparation 1.

δ ($CDCl_3$): 3.13 (s, 3H), 5.32 (s, 2H), 6.77 (d, J=9.0 Hz, 1H), 7.32 (d, J=9.0 Hz, 1H), 7.56 (s, 1H), 8.12 (d, J=7.5 Hz, 2H), 8.24 (d, J=7.5 Hz, 2H).

PREPARATION 12

2-(2,4-Dibromophenoxy)-1-(4-methanesulfonylphenyl)ethanone

Obtained as an off-white solid (85% overall) from 2-bromo-1-(4-methylsulfanylphenyl)ethanone and 2,4-dibromophenol by the procedure described in Preparation 1.

δ ($CDCl_3$): 3.09 (s, 3H), 5.31 (s, 2H), 6.73 (d, J=9.0 Hz, 1H), 7.36 (d, J=9.0 Hz, 1H), 7.69 (s, 1H), 8.08 (d, J=7.5 Hz, 2H), 8.23 (d, J=7.5 Hz, 2H).

PREPARATION 13

2-(2,4-Difluorophenoxy)-1-(4-ethanesulfonylphenyl)ethanone

Obtained as an off-white solid (69% overall) from 2-bromo-1-(4-ethylsulfanylphenyl)ethanone and 2,4-difluorophenol by the procedure described in Preparation 1.

δ ($CDCl_3$): 1.31 (t, J=9.0 Hz, 3H), 3.15 (q, J=9.0 Hz, 2H), 5.31 (s, 2H), 6.70-7.03 (m, 3H), 8.03 (d, J=8.0 Hz, 2H), 8.20 (d, J=8.0 Hz, 2H).

PREPARATION 14

3-(4-Fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one

The title compound of Preparation 2 (0.75 g, 2.43 mmol) was added to a suspension of polyphosphoric acid (7.5 g) in acetic acid (11 ml), pre-heated at 95-100°C. The mixture was heated at 140°C for 4 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 (1:1) as eluent. 3-(4-Fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one was obtained (0.26 g, 11%) as an off-white solid.

δ (DMSO): 2.40 (s, 3H), 3.27 (s, 3H), 6.42 (s, 1H), 6.94-7.04 (m, 2H), 7.06-7.14 (m, 2H), 8.04 (s, 4H).

PREPARATION 15

3-(4-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one

Obtained as an off-white solid (19%) from the tittle compound of Preparation 9 and acetic acid by the procedure described in Preparation 14.

δ ($CDCl_3$): 2.44 (s, 3H), 3.06 (s, 3H), 6.36 (s, 1H) 6.89 (d, J=9.0 Hz,

2H), 7.20 (d, J=9.0 Hz, 2H), 8.00 (d, J=9.0 Hz, 2H), 8.07 (d, J=9.0 Hz, 2H).

PREPARATION 16

Acetic acid 2-(2,4-difluorophenoxy)-1-(4-methanesulfonylphenyl)vinyl ester

Methanesulfonic acid (7.41 g, 77 mmol) was added to a mixture of the title compound of Preparation 1 (10.0 g, 30.7 mmol) and acetic anhydride (20.0 g, 0.196 mol), pre-heated at 80°C. After 2 hours, the reaction was cooled and water (50 ml) was added slowly, maintaining the temperature below 30°C. The mixture was stirred for 30 minutes. The resulting solid was washed with water and dried at 45°C under reduced pressure. Acetic acid 2-(2,4-difluorophenoxy)-1-(4-methanesulfonylphenyl)vinyl ester was obtained (10.2 g, 90%) as a white solid.

δ (DMSO): 2.33 (s, 3H), 3.20 (s, 3H), 7.08-7.16 (m, 1H), 7.40-7.57 (m, 2H), 7.77 (d, J=8.7 Hz, 2H), 7.88 (d, J=8.7 Hz, 2H), 7.89 (s, 1H).

PREPARATION 17

Acetic acid 2-(4-chlorophenoxy)-1-(4-methanesulfonylphenyl)vinyl ester

Obtained as an off-white solid (49%) from the title compound of Preparation 3 and acetic anhydride by the procedure described in Preparation 16.

δ (DMSO): 2.37 (s, 3H), 3.24 (s, 3H), 7.29 (d, J=9.0 Hz, 2H), 7.47 (d, J=9.0 Hz, 2H), 7.82 (d, J=8.7 Hz, 2H), 7.91 (d, J=8.7 Hz, 2H), 7.94 (s, 1H).

PREPARATION 18

Propionic acid 2-(2,4-difluorophenoxy)-1-(4-methanesulfonylphenyl) vinyl ester

Obtained as a white solid (55%) from the title compound of Preparation 1 and propionic anhydride by the procedure described in Preparation 16.

δ ($CDCl_3$): 1.31 (t, J=7.5 Hz, 3H), 2.69 (q, J=7.5 HZ, 2H), 6.87-6.97 (m, 2H), 7.04 (s, 1H), 7.14-7.24 (m, 1H), 7.56 (d, J=8.0 Hz, 2H), 7.92 (d, J=8.0 Hz, 2H).

PREPARATION 19

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

The title compound of Preparation 16 (10.0 g, 27 mmol) was added to a solution of polyphosphoric acid (75 g) in acetic anhydride (10.0 g, 98 mmol), pre-heated at 95-100°C. After 40 minutes, the reaction was cooled at 40-50°C. Methanol/water (1:2) (113 ml) was added, maintaining the temperature below 80°C, and the mixture was stirred 16 hours. The resulting solid was filtered and refluxed in methanol (45 ml) for 2 hours. After cooling, the solid was filtered and recrystallized from methylethylketone, to give 3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (3.86 g, 36%) as an off-white solid.

δ (DMSO): 2.44 (s, 3H), 3.26 (s, 3H), 6.48 (s, 1H), 6.89-6.98 (m, 1H), 7.04-7.14 (m, 1H), 7.34-7.44 (m, 1H), 8.09 (s, 4H).

PREPARATION 20

3-(4-Chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one

Obtained from the title compound of Preparation 17 and acetic anhydride by the procedure described in Preparation 19. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (3:2) as eluent gave 3-(4-chlorophenoxy)-2-(4-methanesulfonylphenyl) -6-methylpyran-4-one (32%) as an off-white solid.

δ (DMSO): 2.44 (s, 3H), 3.26 (s, 3H), 6.48 (s, 1H), 7.20 (d, J=9.0 Hz, 2H), 7.34 (d, J=9.0 Hz, 2H), 8.06 (s, 4H).

PREPARATION 21

5-(2,4-Difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde

Selenium dioxide (7.0 g, 63 mmol) was added to a solution of the title compound of Preparation 19 (5.0 g, 12.7 mmol) in dioxane (55 ml), and the mixture was heated into a sealed tube at 180°C for 60 minutes. After cooling, the crude 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-(2,4-Difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde (2.93 g, 57%) was obtained as an off-white solid.

δ ($CDCl_3$): 3.09 (s, 3H), 6.72-6.83 (m, 1H), 6.88-6.96 (m, 2H), 7.11 (s,

1H), 8.11 (d, J=8.0 Hz, 2H), 8.27 (d, J=8.0 Hz, 2H), 9.80 (s, 1H).

PREPARATION 22

5-(4-Fluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde

Obtained as a brown oil (70% purity, used in the next step without further purification) from the title compound of Preparation 14 by the procedure described in Preparation 21.

δ ($CDCl_3$): 3.09 (s, 3H), 6.90-6.98 (m, 4H), 7.01 (s, 1H), 8.07 (d, J=8.5 Hz, 2H), 8.22 (d, J=8.5 Hz, 2H), 9.82 (s, 1H).

PREPARATION 23

5-(4-Chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde

Obtained as a brown oil (70% purity, used in the next step without further purification) from the title compound of Preparation 20 by the procedure described in Preparation 21.

δ ($CDCl_3$): 3.09 (s, 3H), 6.91 (d, J=8.0 Hz, 2H), 7.15 (s, 1H), 7.29 (d, J=8.0 Hz, 2H), 8.07 (d, J=8.0 Hz, 2H), 8.10 (d, J=8.0 Hz, 2H), 9.83 (s, 1H).

PREPARATION 24

5-(4-Bromophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde

Obtained as a brown oil (80% purity, used in the next step without further purification) from the title compound of Preparation 15 by the procedure described in Preparation 21.

δ ($CDCl_3$): 3.71 (s, 3H), 6.92 (d, J=9.0 Hz, 2H), 7.16 (s, 1H), 7.44 (d, J=9.0 Hz, 2H), 8.05 (d, J=9.0 Hz, 2H), 8.20 (d, J=9.0 Hz, 2H), 9.80(s, 1H).

PREPARATION 25

5-(2-Fluoro-4-bromophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carbaldehyde

Obtained as a brown oil (65% purity, used in the next step without further purification) from the title compound of Example 6 by the procedure described in Preparation 21.

δ ($CDCl_3$): 3.09 (s, 3H), 6.80 (t, J=12.0 Hz, 1H), 7.08-7.20 (m, 1H),

7.11 (s, 1H), 7.25-7.36 (m, 1H), 8.09 (d, J=9.0 Hz, 2H), 8.22 (d, J=9.0 Hz, 2H), 9.80 (s, 1H).

EXAMPLE 1

3-(4-Fluoro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

The title compound of Preparation 4 (11.15 g, 35 mmol) was added to a solution of polyphosphoric acid (115 g) in acetic anhydride (48.7 g, 0.48 mol), pre-heated at 95-100°C. The mixture was heated at the same temperature for 1.5 hours. After cooling, the reaction was poured into ice-water, extracted with ethyl acetate (3 x 200 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 (3:1) as eluent. 3-(4-Fluoro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (2.29 g, 17%) was obtained as an off-white solid.

m.p.: 146°C

δ (DMSO): 2.32 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 6.46 (s, 1H), 6.69-6.72 (m, 1H), 6.83-6.86 (m, 1H), 7.10-7.13 (m, 1H), 8.09 (s, 4H).

EXAMPLE 2

3-(4-Chloro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

Obtained as an off-white solid (15%) from the title compound of Preparation 5 and acetic anhydride by the procedure described in Example 1.

m.p.: 198°C

δ (DMSO): 2.31 (s, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 6.47 (s, 1H), 6.72 (d, J=9.0 Hz, 1H), 7.07 (d, J=9.0 Hz, 1H), 7.32 (s, 1H), 8.08 (s, 4H).

EXAMPLE 3

3-(2-Chloro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

Obtained as an off-white solid (28%) from the title compound of Preparation 6 and acetic anhydride by the procedure described in Example 1.

m.p.: 159°C

δ (DMSO): 2.23 (s, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 6.48 (s, 1H), 6.81

(d, J=8.7 Hz, 1H), 6.98 (d, J=8.7 Hz, 1H), 7.32 (s, 1H), 8.07 (s, 4H).

EXAMPLE 4

3-(2-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one

Obtained as an off-white solid (32%) from the title compound of Preparation 7 and acetic anhydride by the procedure described in Example 1.

m.p.: 197-199°C

δ ($CDCl_3$): 2.46 (s, 3H), 3.11 (s, 3H), 6.43 (s, 1H), 6.67 (d, J=7.5 Hz, 1H), 6.92 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 8.04 (d, J=9.0 Hz, 2H), 8.18 (d, J=9.0 Hz, 2H).

EXAMPLE 5

3-(3-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one

Obtained as an off-white solid (15%) from the title compound of Preparation 8 and acetic anhydride by the procedure described in Example 1.

LRMS: m/z 434 $(M+1)^+$.

δ ($CDCl_3$): 2.45 (s, 3H), 3.09 (s, 3H), 6.40 (s, 1H), 6.91-6.93 (m, 1H), 7.08 (s, 1H), 7.15-7.20 (m, 2H), 8.03 (d, J=8.5 Hz, 2H), 8.07 (d, J=8.5 Hz, 2H).

EXAMPLE 6

3-(4-Bromo-2-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

Obtained as an off-white solid (31%) from the title compound of Preparation 10 and acetic anhydride by the procedure described in Example 1.

m.p.: 215°C

δ ($CDCl_3$): 2.45 (s, 3H), 3.08 (s, 3H), 6.34 (s, 1H), 6.74 (t, J=9.0 Hz, 1H), 7.12 (d, J=9.0 Hz, 1H), 7.29 (d, J=9.0 Hz, 1H), 8.04 (d, J=9.0 Hz, 2H), 8.10 (d, J=9.0 Hz, 2H).

EXAMPLE 7

3-(4-Bromo-2-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

Obtained as an off-white solid (43%) from the title compound of Preparation 11 and acetic anhydride by the procedure described in Example 1.

m.p.: 214-215°C

δ ($CDCl_3$): 2.47 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.58 (d, J=8.5 Hz, 1H), 7.20 (d, J=8.5 Hz, 1H), 7.56 (s, 1H), 8.03 (d, J=7.5 Hz, 2H), 8.12 (d, J=7.5 Hz, 2H).

EXAMPLE 8

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

Obtained as an off-white solid (17%) from the title compound of Preparation 12 and acetic anhydride by the procedure described in Example 1.

m.p.: 231°C

δ ($CDCl_3$): 2.46 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.55 (d, J=9.0 Hz, 1H), 7.25 (d, J=9.0 Hz, 1H), 7.73 (s, 1H), 8.03 (d, J=7.5 Hz, 2H), 8.13 (d, J=7.5 Hz, 2H).

EXAMPLE 9

3-(2,4-Difluorophenoxy)-2-(4-ethanesulfonylphenyl)-6-methyl-pyran-4-one

Obtained as an off-white solid (18%) from the title compound of Preparation 13 and acetic anhydride by the procedure described in Example 1.

m.p.: 154-155°C

δ ($CDCl_3$): 1.30 (t, J=7.5 Hz, 3H), 2.45 (s, 3H), 3.15 (q, J=7.5 Hz, 2H), 6.33 (s, 1H), 6.69-6.76 (m, 1H), 6.81-6.93 (m, 2H), 8.00 (d, J=8.7 Hz, 2H), 8.12 (d, J=8.7 Hz, 2H)

EXAMPLE 10

2-(4-Methanesulfonylphenyl)-6-methyl-3-(2-methylphenoxy)pyran-4-one

To a solution of the title compound of Example 4 (1.40 g, 3.21 mmol) in dimethylformamide (16 ml) were added tetramethyltin (2.40 ml, 17.3 mmol), tri-o-tolylphosphine (0.23 g, 0.77 mmol), palladium acetate (0.043 g, 0.19 mmol) and triethylamine (1.45 ml, 10.3 mmol). The mixture was heated at 105°C for 90 hours. After cooling, the crude material was filtered through Celite® and the solvent was removed under reduced pressure. The resulting oil was dissolved in ethyl acetate (50 ml). The organic solution was washed with water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting oil was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:1) as eluent. 2-(4-Methanesulfonylphenyl)-6-methyl-

3-(2-methylphenoxy)pyran-4-one (0.77 g, 65%) was obtained as an off-white solid.

m.p.: 168°C

δ (DMSO): 2.32 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.65 (d, J=7.5 Hz, 1H), 6.89-6.94 (m, 1H), 6.99-7.02 (m, 1H), 7.22 (d, J=7.5 Hz, 1H), 8.06 (d, J=9.0 Hz, 2H), 8.11 (d, J=9.0 Hz, 2H).

EXAMPLE 11

2-(4-Methanesulfonylphenyl)-6-methyl-3-(3-methylphenoxy)pyran-4-one

Obtained from the title compound of Example 5 by the procedure described in Example 10. Recrystallization from ethanol/water (1:2) gave 2-(4-methanesulfonylphenyl)-6-methyl-3-(3-methylphenoxy)pyran-4-one (0.28 g, 29%) as an off-white solid.

m.p.: 162°C

δ (DMSO): 2.25 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.73-6.85 (m, 3H), 7.13-7.19 (m, 1H), 8.07 (s, 4H).

EXAMPLE 12

3-(2-Fluoro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

Obtained from the title compound of Example 6 by the procedure described in Example 10. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (3:2) as eluent gave 3-(2-fluoro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (64%) as a white solid.

m.p.: 171°C

δ (DMSO): 2.24 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 6.47 (s, 1H), 6.83-6.90 (m, 2H), 7.12 (d, J=12.0 Hz, 1H), 8.08 (s, 4H).

EXAMPLE 13

3-(2,4-Difluorophenoxy)-6-ethyl-2-(4-methanesulfonylphenyl)-5-methyl pyran-4-one

Obtained from the title compound of Preparation 18 and propionic anhydride by the procedure described in Preparation 19. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:2) as eluent gave 3-(2,4-difluorophenoxy)-6-ethyl-2-(4-methane sulfonylphenyl)-5-methylpyran-4-one (21%) as an off-white solid.

m.p.: 200°C

δ (DMSO): 1.29 (t, J=7.5 Hz, 3H), 1.92 (s, 3H), 2.81 (q, J=7.5 Hz, 2H), 3.27 (s, 3H), 6.90-6.96 (m, 1H), 7.02-7.08 (m, 1H), 7.37-7.44 (m, 1H), 8.10 (s, 4H).

EXAMPLE 14

3-Chloro-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one

To a solution of the title compound of Preparation 19 (0.5 g, 1.28 mmol) in dry pyridine (10 ml), was added sulfuryl chloride (0.21 ml, 2.56 mmol) dropwise. The mixture was stirred at room temperature overnight. The crude reaction was poured into ice/2 N hydrochloric acid (75 ml) and extracted with ethyl acetate (2 x 100 ml). The organic phase was washed with water (2 x 50 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (1:2) as eluent. 3-Chloro-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methylpyran-4-one (0.22 g, 40%) was obtained as a white solid.

m.p.: 210°C

δ (DMSO): 2.62 (s, 3H), 3.28 (s, 3H), 6.93-6.99 (m, 1H), 7.17-7.22 (m, 1H), 7.39-7.46 (m, 1H), 8.06-8.10 (m, 4H).

EXAMPLE 15

3-Chloro-5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one

Obtained from the title compound of Preparation 14 by the procedure described in Example 14. Purification by column chromatography with silica gel and methylene chloride/ethyl acetate (9:1) as eluent gave 3-chloro-5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one (20%) as an off-white solid.

m.p.: 279°C

δ (DMSO): 2.62 (s, 3H), 3.27 (s, 3H), 7.05-7.17 (m, 4H), 8.08 (s, 4H).

EXAMPLE 16

3-Chloro-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one

Obtained from the title compound of Preparation 20 by the procedure described in Example 14. Recrystallization from ethanol gave 3-chloro-

5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methylpyran-4-one (45%) as a white solid.

m.p.: 274°C

δ (DMSO): 2.62 (s, 3H), 3.27 (s, 3H), 7.09 (d, J=6.7 Hz, 2H), 7.36 (d, J=6.7 Hz, 2H), 8.07 (s, 4H).

EXAMPLE 17

3-Bromo-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one

To a solution of the title compound of Preparation 19 (5.0 g, 12.7 mmol) in chloroform (100 ml), were added pyridine (1.10 g, 14.0 mmol) and pyridinium tribromide (10.0 g, 28.0 mmol). The mixture was stirred at room temperature for 30 minutes and then refluxed for 92 hours. The crude reaction was diluted with chloroform (100 ml), washed with 2 N hydrochloric acid (2 x 75 ml) and water (2 x 75 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent. 3-Bromo-5-(2,4-difluoro phenoxy)-6-(4-methanesulfonylphenyl)-6-methylpyran-4-one (1.10 g, 18%) was obtained as a white solid.

m.p.: 230°C

δ (DMSO): 2.67 (s, 3H), 3.28 (s, 3H), 6.92-6.99 (m, 1H), 7.12-7.19 (m, 1H), 7.38-7.46 (m, 1H), 8.07 (s, 4H).

EXAMPLE 18

3-Bromo-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one

Obtained from the title compound of Preparation 20 by the procedure described in Example 17. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (2:1) as eluent gave 3-bromo-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methylpyran-4-one (10%) as an off-white solid.

m.p.: 251°C

δ (DMSO): 2.67 (s, 3H), 3.27 (s, 3H), 7.08 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 8.07 (s, 4H).

EXAMPLE 19

3-(2,4-Difluorophenoxy)-5,6-dimethyl-2-(4-methanesulfonylphenyl)pyran-4-one

To a solution of the title compound of Example 17 (0.50 g, 1.1 mmol) in dimethylformamide (10 ml) were added tetramethyltin (0.87 ml, 6.3 mmol), tri-o-tolylphosphine (0.20 g, 0.68 mmol), palladium acetate (0.038 g, 0.17 mmol) and triethylamine (0.30 ml, 2.2 mmol). The mixture was heated at 100°C for 120 hours. After cooling, the crude material was filtered through Celite® and the solvent was removed under reduced pressure. The resulting oil was dissolved in ethyl acetate (50 ml). The organic solution was washed with 2 N hydrochloric acid (2 x 50 ml) and water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting residue was purified by crystallization from isopropyl ether. 3-(2,4-Difluorophenoxy)-5,6-dimethyl-2-(4-methanesulfonylphenyl)pyran-4-one (0.25 g, 58%) as an off-white solid.
m.p.: 192°C
δ (DMSO): 1.90 (s, 3H), 2.47 (s, 3H), 3.27 (s, 3H), 6.89-6.94 (m, 1H), 7.00-7.08 (m, 1H), 7.37-7.43 (m, 1H), 8.09 (s, 4H).

EXAMPLE 20

3-(2,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl-5-vinylpyran-4-one

To a solution of the title compound of Example 17 (0.50 g, 1.1 mmol) in dimethylformamide (10 ml) were added tributylvinyltin (1.24 ml, 4.24 mmol), tri-o-tolylphosphine (0.10 g, 0.34 mmol), palladium acetate (0.019 g, 0.084 mmol) and triethylamine (0.15 ml, 1.1 mmol). The mixture was heated at 100°C overnight. After cooling, the crude material was filtered through Celite® and diluted with ethyl acetate (50 ml). The organic solution was washed with 2 N hydrochloric acid (2 x 50 ml) and water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:3) as eluent. 3-(2,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl-5-vinylpyran-4-one (0.25 g, 57%) was obtained as a white solid.
m.p.: 184°C
δ (DMSO): 2.58 (s, 3H), 3.27 (s, 3H), 5.50 (dd, J=2.4 Hz, J=12.0 Hz, 1H), 6.24 (dd, J=2.4 Hz, J=17.7 Hz, 1H), 6.54 (dd, J=12.0 Hz, J=17.7 Hz, 1H), 6.90-6.96 (m, 1H), 7.10-7.15 (m, 1H), 7.34-7.43 (m, 1H), 8.07-

8.13 (m, 4H).

EXAMPLE 21

3-(2,4-Difluorophenoxy)-5-ethyl-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one

To a solution of the title compound of Example 20 (0.14 g, 0.33 mmol) in ethyl acetate (25 ml) and methanol (50 ml) was added paladium on charcoal (14 mg, 10%). The mixture was hydrogenated at room temperature and at 30 psi for 1 hour. The crude material was filtered through Celite® and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:3) as eluent. 3-(2,4-Difluorophenoxy)-5-ethyl-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (0.063 g, 45%) was obtained as an off-white solid.

m.p.: 173°C

δ (CDCl3): 1.09 (t, J=7.5 Hz, 3H), 2.47 (s, 3H), 2.49 (q, J=7.5 Hz, 2H), 3.09 (s, 3H), 6.72-6.75 (m, 1H), 6.81-6.91 (m, 2H), 8.03 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.5 Hz, 2H).

EXAMPLE 22

3-(2,4-Difluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl) pyran-4-one

To a solution of the title compound of Preparation 21 (1.36 g, 3.3 mmol) in methanol (20 ml), sodium borohydride (0.19 g, 5.2 mmol) 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 dissolved 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 (2:1) as eluent. 3-(2,4-Difluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (0.65 g, 48%) was obtained as a white solid.

m.p.: 205°C

δ (DMSO): 3.27 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.90 (t, J=6.0 Hz, 1H), 6.52 (s, 1H), 6.61-6.67 (m, 1H), 7.07-7.14 (m, 1H), 7.37-7.43 (m, 1H), 8.09 (s, 4H).

EXAMPLE 23

3-(4-Fluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one

Obtained from the title compound of Preparation 22 by the procedure described in Example 22. Recrystallization from ethanol gave 3-(4-fluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (30%) as an off-white solid.

m.p.: 206°C

δ (DMSO): 3.27 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.91 (t, J=6.0 Hz, 1H), 6.52 (s, 1H), 6.98-7.04 (m, 2H), 7.10-7.16 (m, 2H), 8.06 (d, J=8.0 Hz, 2H), 8.10 (d, J=8.0 Hz, 2H).

EXAMPLE 24

3-(4-Chlorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one

Obtained from the title compound of Preparation 23 by the procedure described in Example 22. Recrystallization from ethanol gave 3-(4-chlorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (49%) as an off-white solid.

m.p.: 227°C

δ (DMSO): 3.26 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.91 (t, J=6.0 Hz, 1H), 6.53 (s, 1H), 7.04 (d, J=7.0 Hz, 2H), 7.34 (d, J=7.0 Hz, 2H), 8.07 (s, 4H).

EXAMPLE 25

3-(2-Fluoro-4-bromophenoxy)-6-hydroxymethyl-2-(4-methanesulfonyl phenyl)pyran-4-one

Obtained from the title compound of Preparation 24 by the procedure described in Example 22. Purification by column chromatography with silica gel and ethyl acetate gave 3-(2-fluoro-4-bromophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one (34%) as an off-white solid.

m.p.: 202-203°C

δ ($CDCl_3$):3.08 (s, 3H), 4.64 (s, 2H), 6.62 (s, 1H), 6.74 (t, J=8.9 Hz, 1H), 7.12 (dd, J=1.5 Hz, J=8.9 Hz, 1H), 7.29 (dd, J=2.4 Hz, J=10.5, 1H), 8.02 (d, J=8.9 Hz, 2H), 8.08 (d, J=8.9 Hz, 2H).

EXAMPLE 26

3-(2,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethyl pyran-4-one

To a solution of the title compound of Example 22 (0.64 g, 1.6 mmol) in methylene chloride (30 ml) and tetrahydrofuran (20 ml) were added methyl iodide (0.29 ml, 4.7 mmol) and a solution of sodium hydroxide (0.50 g, 12.5 mmol) and tetrabutylammonium chloride (50 mg) in water (1 ml). The reaction mixture was stirred at room temperature for 18 hours. The organic layer was diluted with methylene chloride (30 ml), washed with water, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The resulting solid was purified by column chromatography with silica gel and methylene chloride/ethyl acetate/acetic acid (78:10:1) as eluent. 3-(2,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one (0.09 g, 14%) was obtained as an off white solid.

m.p.: 124°C

δ (DMSO): 3.27 (s, 3H), 3.43 (s, 3H), 4.47 (s, 2H), 6.57 (s, 1H), 6.70-6.94 (m, 1H), 7.10-7.18 (m, 1H), 7.39-7.43 (m, 1H), 8.06 (d, J=9.0 Hz, 2H), 8.11 (d, J=9.0 Hz, 2H).

EXAMPLE 27

3-(4-Fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one

To a solution of the title compound of Example 23 (0.74 g, 0.9 mmol) in methanol (50 ml) were added methyl iodide (0.36 ml, 5.8 mmol) and freshly prepared silver oxide (1.75 g, 7.59 mmol). The reaction mixture was stirred at room temperature for 18 hours. The crude material was filtered through Celite® and washed with methanol (3 x 25 ml). The organic solution was washed with diluted ammonium hydroxide (2 x 50 ml) and water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and methylene chloride/ethyl acetate/acetic acid (78:10:1) as eluent. 3-(4-Fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one (0.40 g, 52%) was obtained as a white solid.

m.p.: 165°C

δ (DMSO): 3.27 (s, 3H), 3.43 (s, 3H), 4.48 (s, 2H), 6.57 (s, 1H), 7.05-7.13 (m, 4H), 8.07 (s, 4H).

EXAMPLE 28

3-(4-Chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one

Obtained from the title compound of Example 24 by the procedure described in Example 27. Purification by column chromatography with silica gel and methylene chloride/ethanol/ammonium hydroxide (100:8:1) as eluent gave 3-(4-chlorophenoxy)-2-(4-methanesulfonyl phenyl)-6-methoxymethylpyran-4-one (49%) as an off-white solid.

m.p.: 156°C

δ (DMSO): 3.26 (s, 3H), 3.42 (s, 3H), 4.47 (s, 2H), 6.58 (s, 1H), 7.05 (d, J=7.5 Hz, 2H), 7.35 (d, J=7.5 Hz, 2H), 8.04 (d, J=9.0 Hz, 2H), 8.08 (d, J=9.0 Hz, 2H).

EXAMPLE 29

Acetic acid [5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester

To a solution of the title compound of Example 22 (0.75 g, 1.8 mmol) in methylene chloride (10 ml) were added triethyl amine (0.28 ml, 2.0 mmol) and acetyl chloride (0.14 ml, 2.02 mmol). The mixture was stirred at room temperature for 4 hours. The crude material was poured into ice and diluted with methylene chloride (50 ml). The organic solution was washed with sodium bicarbonate (4%, 2 x 50 ml) and water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:1) as eluent. Acetic acid [5-(2,4-difluorophenoxy)-6-(4-methanesulfonyl phenyl)-4-oxo-4H-pyran-2-yl]methyl ester (0.39 g, 47%) was obtained as a white solid.

m.p.: 175°C

δ (DMSO): 2.17 (s, 3H), 3.28 (s, 3H), 5.14 (s, 2H), 6.68 (s, 1H), 6.94-6.97 (m, 1H), 7.09-7.16 (m, 1H), 7.36-7.44 (m, 1H), 8.06-8.12 (m, 4H)

EXAMPLE 30

Acetic acid [5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester

Obtained from the title compound of Example 23 by the procedure described in Example 29. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (3:2) as eluent gave acetic acid

[5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester (47%) as an off-white solid.

m.p.: 180°C

δ (DMSO): 2.17 (s, 3H), 3.27 (s, 3H), 5.14 (s, 2H), 6.69 (s, 1H), 7.01-7.06 (m, 2H), 7.10-7.16 (m, 2H), 8.08 (s, 4H).

EXAMPLE 31

Acetic acid [5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester

Obtained from the title compound of Example 24 by the procedure described in Example 29. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave acetic acid [5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester (47%) as an off-white solid.

m.p.: 115°C

δ (DMSO): 2.17 (s, 3H), 3.27 (s, 3H), 5.15 (s, 2H), 6.69 (s, 1H), 7.05 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 8.07 (s, 4H).

EXAMPLE 32

5-(2,4-Difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid

To a cooled solution of the title compound of Preparation 21 (1.50 g, 3.69 mmol) in acetone (6 ml) was added a solution of chromium (VI) oxide (0.41 g, 4.1 mmol) and sulfuric acid (3.5 ml) in water (3 ml). The mixture was stirred at 0°C for 1 hour and at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (50 ml). The organic solution was washed with water and with 2 N sodium hydroxide (2 x 50 ml). The basic phase was acidified with 2 N hydrochloric acid and extracted with ethyl acetate (2 x 50 ml). The combined organic extracts were washed with water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting solid was recrystallized from ethanol to give 5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid (0.20 g, 13%) as a white solid.

m.p.: 245°C

δ (DMSO): 3.28 (s, 3H), 6.93-6.98 (m, 1H), 7.12 (s, 1H), 7.14-7.24 (m, 1H), 7.39-7.46 (m, 1H), 8.09 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.5 Hz, 2H).

EXAMPLE 33

5-(4-Chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid

Obtained from the title compound of Preparation 23 by the procedure described in Example 32. Recrystallization from ethyl acetate gave 5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid (25%) as an off-white solid.

m.p.: 263°C

δ (DMSO): 3.27 (s, 3H), 7.11 (d, J=9.0 Hz, 2H), 7.12 (s, 1H), 7.35 (d, J=9.0 Hz, 2H), 8.05-8.10 (m, 4H).

EXAMPLE 34

6-(1,1-Difluoromethyl)-3-(2,4-difluorophenoxy)-2-(4-methanesulfonyl phenyl)pyran-4-one

To a cooled solution of the title compound of Preparation 21 (1.0 g, 2.5 mmol) in methylene chloride (15 ml) was added (diethylamino)sulfur trifluoride (0.39 ml, 2.9 mmol). The mixture was stirred at 0°C for 1 hour and at room temperature for 16 hours. The mixture was diluted with methylene chloride (50 ml). The organic solution was washed with water (2 x 50 ml), dried (Na_2SO_4), and the solvent removed under reduced pressure. The resulting residue was purified by column chromatography with silica gel and ethyl acetate/n-hexane (2:3) as eluent. 6-(1,1-Difluoromethyl)-3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)pyran-4-one (0.20 g, 18%) as an off-white solid.

m.p.: 156°C

δ (DMSO): 3.28 (s, 3H), 6.93-6.99 (m, 1H), 7.00 (s, 1H), 7.12 (t, J_{F-H}=54 Hz, 1H), 7.22-7.30 (m, 1H), 7.38-7.46 (m, 1H), 8.07 (d, J=9.0 Hz, 2H), 8.12 (d, J=9.0 Hz, 2H).

EXAMPLE 35

6-(1,1-Difluoromethyl)-3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl) pyran-4-one

Obtained from the title compound of Preparation 24 by the procedure described in Example 34. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:1) as eluent gave 6-(1,1-difluoromethyl)-3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)pyran-4-one (0.58, 48%) as an off-white solid.

LRMS: m/z 471 $(M+1)^+$.

δ ($CDCl_3$): 3.08 (s, 3H), 6.53 (t, J_{F-H}=78 Hz, 1H), 6.85 (d, J=9.0 Hz, 2H), 7.40 (d, J=9.0 Hz, 2H), 8.00-8.11 (m, 4H).

EXAMPLE 36

6-(1,1-Difluoromethyl)-2-(4-methanesulfonylphenyl)-3-(4-methyl phenoxy)pyran-4-one

Obtained from the title compound of Example 35 by the procedure described in Example 10. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (2:3) as eluent gave 6-(1,1-difluoromethyl)-2-(4-methanesulfonylphenyl)-3-(4-methylphenoxy)pyran-4-one (0.20 g, 18) as an off-white solid.

m.p.: 160°C

δ (DMSO): 2.23 (s, 3H), 3.26 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 6.98 (s, 1H), 7.09 (d, J=9.0 Hz, 2H), 7.11 (t, J_{F-H}=54 Hz, 1H), 8.04-8.11 (m, 4H).

EXAMPLE 37

3-Bromo-2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methane sulfonylphenyl)pyran-4-one

Obtained from the title compound of Example 34 by the procedure described in Example 17. Purification by column chromatography with silica gel and ethyl acetate/n-hexane (1:2) as eluent gave 3-bromo-2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methanesulfonyl phenyl)pyran-4-one (13%) as an off-white solid.

LRMS: m/z 507 $(M+1)^+$.

δ (DMSO): 3.13 (s, 3H), 6.71-7.13 (m, 4H), 8.11 (d, J=9.0 Hz, 2H), 8.25 (d, J=9.0 Hz, 2H).

EXAMPLE 38

2-(1,1-Difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methanesulfonyl phenyl)-3-methylpyran-4-one

Obtained from the title compound of Example 37 by the procedure described in Example 19. Recrystallization from ethanol gave 2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-3-methylpyran-4-one (86%) as an off-white solid.

m.p.: 187.8-188.6°C

δ ($CDCl_3$): 2.14 (s, 3H), 3.09 (s,3H), 6.56-6.93 (m, 4H), 8.07 (d, J=8.7 Hz, 2H), 8.19 (d, J=8.7 Hz, 2H).

Examples 39 and 40 illustrate pharmaceutical compositions according to the present invention and procedure for their preparation.

EXAMPLE 39

Capsules

25,000 capsules each containing 100 mg of 3-(4-fluoro-2-methylphenoxy)-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 40

Tablets

100,000 Tablets each containing 50 mg of 3-(2,4-difluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-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

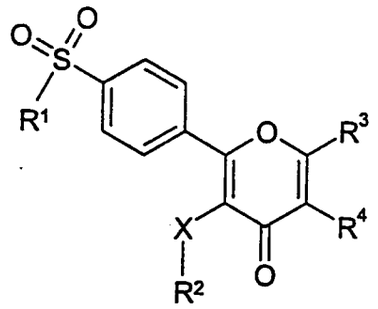
Procedure

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 $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkyl, hydroxymethyl, alkoxymethyl, alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

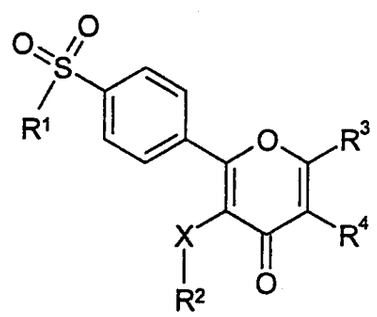
R^4 represents a hydrogen atom, or an alkyl, alkenyl or alkynyl group or a halogen atom; and

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

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (I):

(I)



wherein:

R^1 represents an alkyl or $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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;

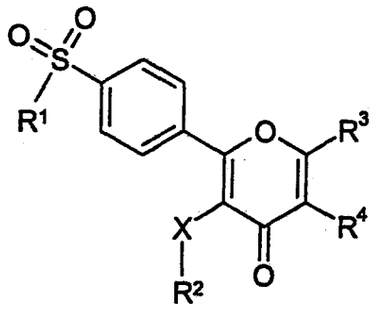
R^3 represents an alkyl, hydroxymethyl, alkoxymethyl, alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents a hydrogen atom, or an alkyl, alkenyl or alkynyl group or a halogen atom; and

X represents a single bond, an oxygen atom, a sulfur atom or a methylene group; with the proviso that when R^4 is a hydrogen atom R^3 is an alkenylmethoxymethyl, C_3-C_7 cycloalkylmethoxymethyl or R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

or a pharmaceutically acceptable salt thereof.

3. A compound of formula (I):



(I)

wherein:

R^1 represents an alkyl or $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkyl, hydroxymethyl, alkoxymethyl,

alkenyloxymethyl, C_3-C_7 cycloalkoxymethyl, C_3-C_7 cycloalkylmethoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

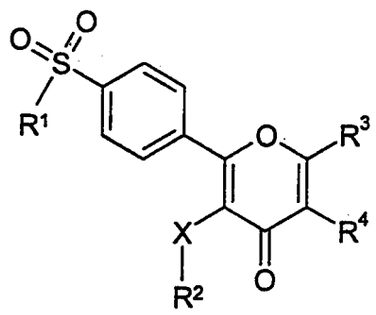
R^4 represents an alkyl, alkenyl or alkynyl group or a halogen atom; and

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

or a pharmaceutically acceptable salt thereof.

4. A compound of formula (I):

(I)



wherein:

R^1 represents an alkyl or $-NR^5R^6$ group, wherein R^5 and R^6 each independently represent 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 an alkenyloxymethyl or C_3-C_7 cycloalkylmethoxymethyl group or a R^7-COO-CH_2- group wherein R^7 represents an alkyl or phenyl group;

R^4 represents a hydrogen atom; and

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

or a pharmaceutically acceptable salt thereof.

5. A compound according to any one of claims 2 to 4 wherein R^1 represents an unsubstituted alkyl group or NH_2.

6. A compound according to claim 5 wherein R^1 is a methyl group.

7. A compound according to any one of claims 2 to 6 wherein X represents an oxygen atom.

8. A compound according to any one of claims 2, 3, 5, 6 or 7 wherein R^3 represents an unsubstituted C_{1-3} alkyl, hydroxymethyl, methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, difluoromethyl, propenyloxymethyl, hydroxycarbonyl, cyclopropoxy methyl, cyclobutoxymethyl, cyclopropylmethoxymethyl, cyclobutyl methoxymethyl or CH_3-COO-CH_2- group.

9. A compound according to any one of claims 2 to 8 wherein R^3 is a propenyloxymethyl, cyclopropylmethoxymethyl, cyclobutylmethoxy methyl or CH_3-COO-CH_2- group.

10. A compound according to any one of claims 2, 3, 5, 6, 7, 8 or 9 wherein R^4 is a chlorine or bromine atom or a methyl, ethyl, ethenyl or ethynyl group.

11. A compound according to any one of claims 2 to 10 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.

12. A compound according to any one of claims 2 to 11 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.

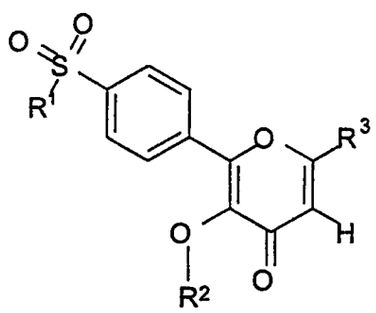
13. A compound according to any one of claims 2 to 12 wherein R^2 represents a phenyl group substituted by 1 or 2 substituents independently selected from halogen atoms and methyl groups.

14. A compound according to any one of claims 2 to 13 wherein R^2 is a 2,4-difluorophenyl group.

15. A compound according to any one of claims 2 to 14 which is:
3-(2,4-difluorophenoxy)-6-ethyl-2-(4-methanesulfonylphenyl)-5-methyl

pyran-4-one;
3-chloro-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-chloro-5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-chloro-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-bromo-5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-2-methyl pyran-4-one;
3-bromo-5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-2-methylpyran -4-one;
3-(2,4-difluorophenoxy)-5,6-dimethyl-2-(4-methanesulfonylphenyl)pyran -4-one;
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methyl-5-vinyl pyran-4-one;
3-(2,4-difluorophenoxy)-5-ethyl-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-bromo-2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methane sulfonylphenyl)pyran-4-one;
2-(1,1-difluoromethyl)-5-(2,4-difluorophenoxy)-6-(4-methanesulfonyl phenyl)-3-methylpyran-4-one;
acetic acid [5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
acetic acid [5-(4-fluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
acetic acid [5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-yl]methyl ester;
or a pharmaceutically acceptable salt thereof.

16. A compound of formula (IA):



(IA)

wherein:

R^1 represents a methyl or ethyl group;

R^2 represents a phenyl group which may be unsubstituted or substituted by one or more substituents selected from halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^3 represents an alkyl, hydroxymethyl, alkoxymethyl, C_3-C_7 cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group;

provided that when R^3 is methyl, R^2 is either (a) a phenyl group having at least one substituent selected from trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups, (b) a monosubstituted phenyl group having a halogen atom or an alkyl group at the 3-position or having a bromine atom or an alkyl group at the 2-position, (c) a phenyl group having two or more substituents wherein at least one substituent is a bromine atom or wherein an alkyl group is present at the 2- or 4-position, or (d) 3-methyl-4-fluoro-phenyl;

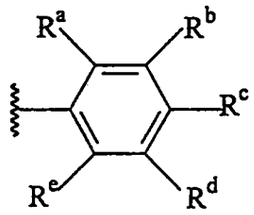
or a pharmaceutically acceptable salt thereof.

17. A compound according to claim 16 wherein R^3 is an ethyl, propyl, hydroxymethyl, methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, difluoromethyl, hydroxycarbonyl, cyclopropoxymethyl or cyclobutoxymethyl group.

18. A compound according to claim 16 or 17 wherein R^3 is a hydroxymethyl, methoxymethyl or hydroxycarbonyl group.

19. A compound according to claim 17 or 18 wherein R^2 is an unsubstituted phenyl group or a phenyl group substituted by a single halogen atom selected from fluorine, chlorine or bromine, a single methyl group or two halogen atoms which are the same or different and are selected from fluorine, chlorine or bromine.

20. A compound according to claim 19 wherein R^2 represents a group of formula

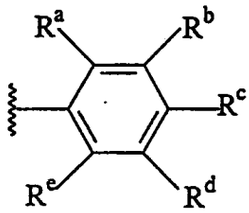


wherein R^a, R^b, R^c, R^d and R^e are defined as follows

R^a	R^b	R^c	R^d	R^e
H	H	H	H	H
H	H	F	H	H
H	F	H	H	H
F	H	H	H	H
H	H	Cl	H	H
H	Cl	H	H	H
Cl	H	H	H	H
H	H	Br	H	H
H	Br	H	H	H
Br	H	H	H	H
H	H	Me	H	H
H	Me	H	H	H
Me	H	H	H	H
F	H	F	H	H
F	H	H	F	H
H	F	F	H	H
F	H	H	H	F
Cl	H	Cl	H	H
Cl	H	H	Cl	H
H	Cl	Cl	H	H
Cl	H	H	H	Cl
F	H	Cl	H	H
Cl	H	F	H	H
F	H	Br	H	H
Cl	H	Br	H	H
Br	H	Br	H	H

Br	H	F	H	H
H	Cl	F	H	H
H	F	Cl	H	H
F	H	Me	H	H
Cl	H	Me	H	H
Me	H	F	H	H
Me	H	Cl	H	H
H	Me	F	H	H
H	Me	Cl	H	H
H	F	Me	H	H
H	Cl	Me	H	H

21. A compound according to claim 16 wherein R^3 is methyl and R^2 is a group of formula



wherein R^a, R^b, R^c, R^d and R^e are defined as:

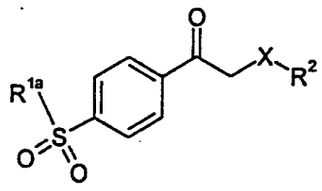
R^a	R^b	R^c	R^d	R^e
H	Br	H	H	H
Br	H	H	H	H
H	Me	H	H	H
Me	H	H	H	H
Me	H	F	H	H
Me	H	Cl	H	H
F	H	Me	H	H
Cl	H	Me	H	H
H	Me	F	H	H
H	F	Me	H	H
H	Cl	Me	H	H
F	H	Br	H	H
Cl	H	Br	H	H
Br	H	Br	H	H

22. A compound according to claim 16 which is
3-(4-fluoro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-(4-chloro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-(2-chloro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-(2-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one;
3-(3-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one;
3-(4-bromo-2-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran -4-one;
3-(4-bromo-2-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran -4-one;
3-(2,4-dibromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one;
3-(2,4-difluorophenoxy)-2-(4-ethanesulfonylphenyl)-6-methylpyran-4-one;
2-(4-methanesulfonylphenyl)-6-methyl-3-(2-methylphenoxy)pyran-4-one;
2-(4-methanesulfonylphenyl)-6-methyl-3-(3-methylphenoxy)pyran-4-one;
3-(2-fluoro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methyl pyran-4-one;
3-(2,4-difluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl) pyran-4-one;
3-(4-fluorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one;
3-(4-chlorophenoxy)-6-hydroxymethyl-2-(4-methanesulfonylphenyl)pyran-4-one;
3-(2-fluoro-4-bromophenoxy)-6-hydroxymethyl-2-(4-methanesulfonyl phenyl)pyran-4-one;
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethyl pyran-4-one;
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran -4-one;
3-(4-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one;
5-(2,4-difluorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid;
5-(4-chlorophenoxy)-6-(4-methanesulfonylphenyl)-4-oxo-4H-pyran-2-carboxylic acid;
6-(1,1-difluoromethyl)-3-(2,4-difluorophenoxy)-2-(4-methanesulfonyl phenyl)pyran-4-one;

6-(1,1-difluoromethyl)-3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl) pyran-4-one;
6-(1,1-difluoromethyl)-2-(4-methanesulfonylphenyl)-3-(4-methyl phenoxy)pyran-4-one;
or a pharmaceutically acceptable salt thereof.

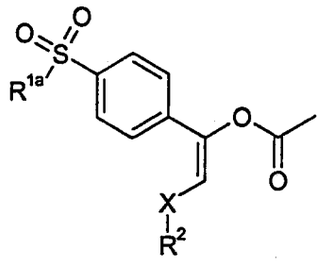
23. A process for producing a compound of formula (I) as defined in any one of claims 1 to 15 or a compound of formula (IA) as defined in any one of claims 16 to 22 which process comprises:
(a) wherein R^1 is an alkyl or $-NR^5R^6$ group in which R^5 and R^6 is each independently an alkyl group, R^3 is a methyl group, R^4 is a hydrogen atom and R^2 and X are as
defined in the previous claims,
ai) reacting a carbonyl derivative of formula (III):

(III)



wherein R^{1a} is an alkyl or a $-NR^{5a}R^{6a}$ group in which R^{5a} and R^{6a} are each independently alkyl groups and R^2 and X are as defined in the previous claims, with an excess of anhydrous acetic acid or acetic anhydride and polyphosphoric acid, at a temperature from 90°C to 150°C; or
aii) reacting a vinyl derivative of formula (IV):

(IV)



wherein R^{1a}, R^2 and X are as defined above, with an excess of acetic anhydride and polyphosphoric acid at a temperature from 80°C to 120°C;
(b) wherein R^1 is an alkyl or $-NR^5R^6$ group in which R^5 and R^6 are alkyl groups, R^4 is an alkyl group, R^3 is an alkyl group of formula CH_2-R^4 and R^2 and X are as defined in the previous claims,
bi) reacting a carbonyl derivative of formula (III) with an excess of

an anhydride of formula (IX):

(IX) $(R^{4a}CH_2CO)_2O$

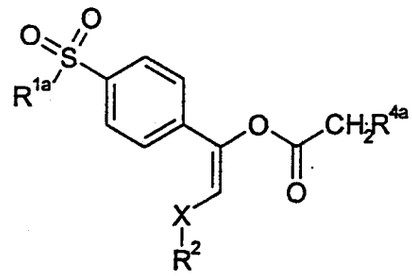
or a carboxylic acid of formula (X):

(X) $R^{4a}CH_2COOH$

and polyphosphoric acid at a temperature from 90°C to 150°C; or

bii) reacting a vinyl derivative of formula (XI):

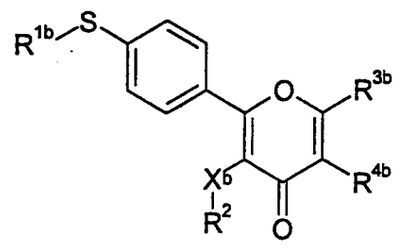
(XI)



wherein R^{1a}, R^2, R^4 and X are as defined above with an excess of an anhydride of formula (IX) and polyphosphoric acid at a temperature from 90°C to 150°C;

(c) wherein R^1 is an alkyl group, R^3 is an alkyl group, R^4 is a hydrogen atom or an alkyl group, and X is as defined in any of claims 1 to 22 with the proviso that it is other than a sulfur atom and R^2 is as defined in any one of claims 1 to 22, by reacting a mercapto derivative of formula (XIII):

(XIII)

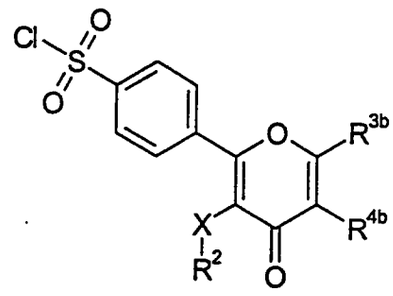


wherein R^{1b} is an alkyl group, R^{3b} is a methyl group or a $R^{4b}CH_2$ group, R^{4b} is a hydrogen atom or an alkyl group X^b is as defined for X in any one of claims 1 to 22 with the proviso that it is other than a sulfur atom and R^2 is as defined above, with an oxidising agent;

(d) Wherein R^1 is a $-NR^5R^6$ group, R^3 is an alkyl group, R^4 is a hydrogen

atom or an alkyl group, R^2, R^5, R^6 and X are as defined in claims 1 to 22 by reacting a chlorosulfonyl derivative of formula (XV):

(XV)



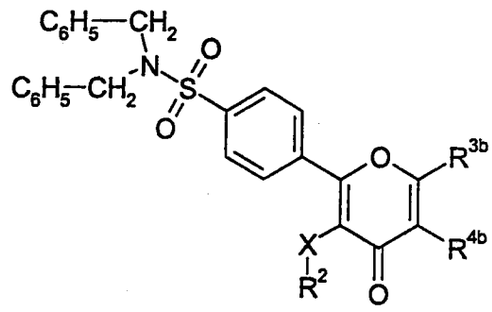
wherein R^2, R^{3b}, R^{4b} and X are as defined above with an amine of formula (XVI):

(XVI) R^5-NH-R^6

wherein R^5 and R^6 are as defined above;

(e) wherein R^1 is a $-NR^5R^6$ group wherein R^5 and R^6 are hydrogen, R^3 is an alkyl group and R^4 is an hydrogen atom or an alkyl group, by debenzylation of the corresponding N,N-dibenzyl derivative of formula (XIX):

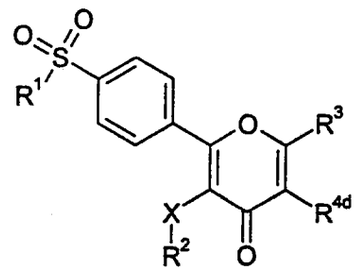
(XIX)



wherein R^2, R^{3b}, R^{4b} and X are as defined above;

(f) wherein R^4 is other than a hydrogen atom, reacting a compound of formula (XXXIII):

(XXXIII)



wherein R^{4d} is a chlorine, bromine or iodine atom, preferably a bromine atom and R^1, R^2, R^3 and X are as defined in the previous claims, with a tin derivative of formula (XXXIV):

(XXXIV) $R^{4c}\ Sn\ (R^9)_3$

wherein R^{4c} is an alkyl, alkenyl or alkynyl group and R^9 is an alkyl group.

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

25. A compound according to any one of claims 1 to 22 or a composition according to claim 24 for use in a method of treatment of the human or animal body by therapy.

26. Use of a compound according to any one of claims 1 to 22 or a composition according to claim 24 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.

27. A method for treating pain, fever or inflammation inhibiting prostanoid-induced smooth muscle contraction or treating 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 22 or a composition according to claim 24.

DERIVADOS DE 2-FENILPIRAN-4-ONA

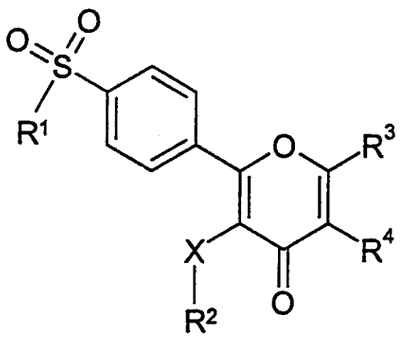
La presente invención se refiere a nuevos derivados terapéuticamente útiles de 2-fenilpiran-4-ona, a procedimientos para su preparación y a composiciones farmacéuticas que los contienen.

Es conocido que la inhibición no selectiva de la enzima ciclooxigenasa (COX) evita la superproducción de prostaglandinas asociadas con inflamación, las cuales estan mediadas por ciclooxigenasa-2 (COX-2) pero, al mismo tiempo, priva a los tejidos de niveles basales de prostaglandinas necesarias para la salud de ciertos tejidos, mediados ampliamente por ciclooxigenasa-1 (COX-1). Los fármacos antiinflamatorios no esteroidales son inhibidores no selectivos de COX y por esta razón, tienen efectos secundarios de dismunición del flujo renal, disminución de la función plaquetaria, dispepsia y ulceración gástrica.

Nosotros hemos encontrado ahora que ciertos derivados de 2-fenilpiran-4-ona inhiben selectivamente la COX-2, en preferencia a la COX-1, y son útiles en el tratamiento de enfermedades mediadas por la COX-2 tales como inflamación, dolor, fiebre, y asma con efectos secundarios mínimos.

De acuerdo con esto, la presente invención se refiere a un compuesto 2-fenilpiran-4-ona de fórmula (I):

(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo

el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquil metoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un átomo de hidrógeno, o un grupo alquilo, alquenilo, alquinilo o un átomo de halógeno; y

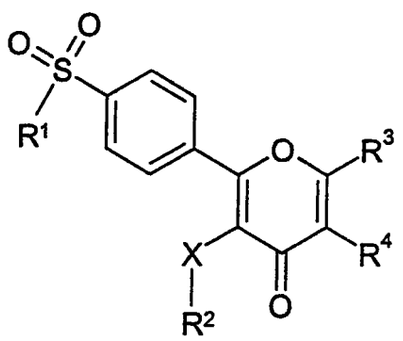
X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

En los compuestos de fórmula (I), donde R^3 es un grupo alqueniloximetilo, es típicamente un grupo alquenilmetoximetilo.

En un aspecto preferido, la presente invención se refiere a un compuesto de fórmula (I):

(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquilmetoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

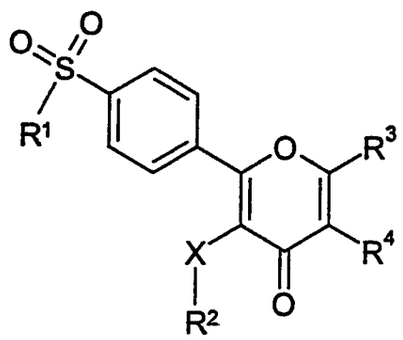
R^4 representa un átomo de hidrógeno, o un grupo alquilo, alquenilo o alquinilo o un átomo de halógeno; y

X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno; con la condición de que cuando R^4 es un átomo de hidrógeno, R^3 es un grupo alquenilmetoximetil, C_3-C_7 cicloalquilmetoximetilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo; o una sal farmacéuticamente aceptable de los mismos.

En este aspecto preferido, cuando R^3 es un grupo alqueniloximetilo, es típicamente un grupo alquenilmetoximetilo.

En otro aspecto preferido, la presente invención se refiere a un compuesto de fórmula (I):

(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquil metoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un grupo alquilo, alquenilo o alquinilo o un átomo de halógeno; y

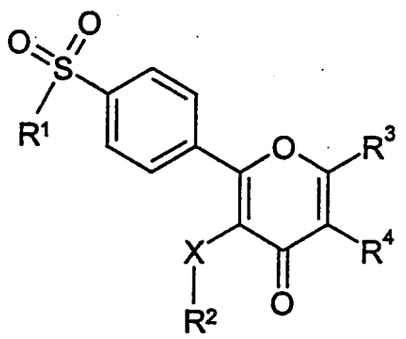
X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

En este aspecto preferido adicional, cuando R^3 es un grupo alqueniloximetilo, es típicamente un grupo alquenilmetoximetilo.

En otro aspecto preferido, la presente invención se refiere a un compuesto de fórmula (I):

(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alqueniloximetilo o C_3-C_7 cicloalquilmetoximetilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un átomo de hidrógeno; y

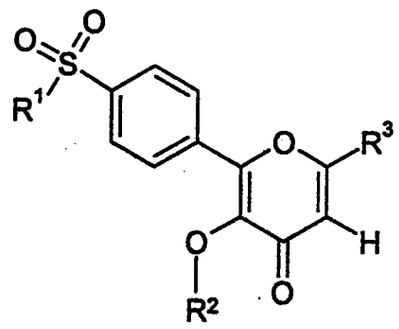
X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

En este aspecto preferido adicional, cuando R^3 es un grupo alqueniloximetilo, es típicamente un grupo alquenilmetoximetilo.

En otro aspecto preferido, la presente invención se refiere a un compuesto de fórmula (IA):

(IA)



en donde:

R^1 representa un grupo metilo o etilo;

R^2 representa un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más sustituyentes seleccionados entre átomos de halógeno o grupos alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, C_3-C_7 cicloalcoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo;

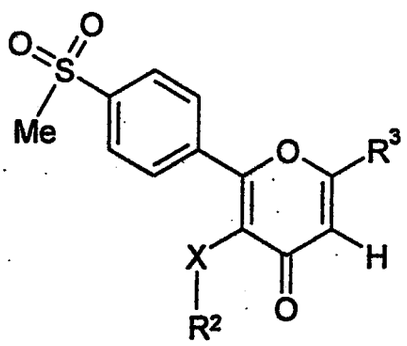
a condición de que cuando R^3 es metilo, R^2 es (a) un grupo fenilo que tiene al menos un sustituyente seleccionado entre los grupos trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo, (b) un grupo fenilo monosustituido que tiene un átomo de halógeno o un grupo alquilo en la posición 3 o que tiene un átomo de bromo o un grupo alquilo en la posición 2 o (c) un grupo fenilo que tiene dos o más sustituyentes en donde al menos un sustituyente es un átomo de bromo o en donde un grupo alquilo está presente en la posición 2 o 4, (d) 3-metil-4-fluorofenilo,

o una sal farmacéuticamente aceptable de los mismos.

En los compuestos de fórmula (IA), R^1 es típicamente un grupo metilo. Además, cuendo R^3 es un grupo metilo, R^2 es típicamente fenilo que tiene al menos un sustituyente seleccionado entre los grupos trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo; siendo el sustituyente preferentemente seleccionado entre los grupos hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo.

La invención también se refiere a un compuesto de fórmula (IB):

(IB)



en donde:

R^2 representa un grupo fenilo que puede estar no sustituido o sustituido por uno o más átomos de halógeno o grupos alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, C_3-C_7 cicloalcoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo;

o una sal farmacéuticamente aceptable de los mismos.

En las fórmulas (IA) y (IB), R^3 es típicamente un grupo hidroximetilo, metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, difluorometilo, hidroxicarbonilo, ciclopropoximetilo o ciclobutoximetilo.

Los grupos alquilo y radicales como alcoxi, hidroxialquilo, mono- o di-alquilamino, mencionados en relación a los grupos R^1 a R^7 son normalmente alquilo "inferior" es decir que contienen de 1 a 6 especialmente de 1 a 4 átomos de carbono, siendo la cadena hidrocarbonada lineal o ramificada. Los grupos alquilo preferidos

y los radicales alquilo más relevantes, incluyen metilo, etilo, propilo incluyendo i-propilo, y butilo incluyendo n-butilo, t-butilo y sec-butilo.

En un grupo fenilo sustituído por uno o más átomos de halógeno o grupos alquilo, trifluoroalquilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquil amino, hidroxialquilo o hidroxicarbonilo, el anillo de fenilo puede estar sustituído por 1, 2, 3, 4 o 5 sustituyentes, preferentemente 1, 2 o 3 sustituyentes, siendo cada uno independientemente seleccionados de los posibles sustituyentes mencionados anteriormente. Es decir, el grupo fenilo (unido a X o al anillo piran-4-ona a través de su posición 1) puede estar sustituido en cualquiera de las posiciones restantes, es decir las posiciones 2, 3, 4, 5 o 6. Un grupo fenilo teniendo más de un sustituyente puede estar sustituido en cualquier combinación de posiciones. Por ejemplo un grupo fenilo teniendo dos sustituyentes puede estar sustituido en las posiciones 2 y 3, 2 y 4, 2 y 5, 2 y 6, 3 y 4 o 3 y 5.

En particular, es preferido que R^2 represente un grupo alquilo ramificado, C_3-C_7 (preferentemente C_3, C_5 or C_6) cicloalquilo, naftilo, tetrahidronaftilo o indanilo, un grupo fenilo no sustituido o un grupo fenilo sustituido por uno o más átomos de halógeno, grupos alquilo, preferentemente grupos metilo, y/o grupos alcoxi, preferentemente grupos metoxi. Los átomos de halógeno son preferentemente seleccionados de átomos de flúor, cloro o bromo.

Es preferido que R^2 represente un grupo fenilo, no sustituido o sustituido preferentemente con 1, 2 o 3 sustituyentes, más preferentemente 1 o 2 sustituyentes. Preferentemente los sustituyentes son independientemente seleccionados de grupos metilo y átomos de cloro, bromo y flúor. Cuando R^2 es un grupo fenilo sustituido por uno o más átomos de halógeno y/o grupos alquilo, preferentemente una de las sustituciones está en la posición 2 o 3 del grupo fenilo.

En un grupo preferido de compuestos, R^2 es un grupo fenilo no sustituido o un grupo fenilo sustituido por un átomo de halógeno seleccionado de flúor, cloro o bromo, un grupo metilo o dos átomos

de halógeno iguales o diferentes y seleccionados de flúor, cloro o bromo.

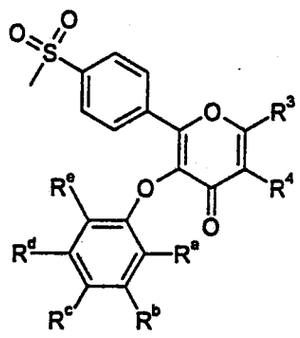
Es preferido que R^1 represente independientemente un grupo alquilo no sustituido como un grupo metilo, etilo, propilo o butilo, preferentemente un grupo metilo o un grupo NH_2 (es decir R^5 y R^6 en la fórmula anterior ambos independientemente representan un átomo de hidrógeno).

Es también preferido que R^3 independientemente represente un grupo C_{1-3} alquilo no sustituido como un grupo metilo, etilo, o n-propilo o i-propilo, un grupo nitrilo, un grupo hidroximetilo, un grupo metoximetilo, un grupo etoximetilo, un grupo propoximetilo, un grupo isopropoximetilo, un grupo difluorometilo, un grupo propeniloximetilo, un grupo hidroxicarbonilo, un grupo ciclopropoximetilo, un grupo ciclobutoximetilo, un grupo ciclopropilmetoximetilo, un grupo ciclobutilmetiloximetil o un grupo CH_3-COO-CH_2-.

Es preferido que R^4 represente un grupo alquilo tal como metilo o etilo, un grupo alquenilo tal como vinilo, un grupo alquinilo tal como etinilo, un átomo de halógeno tal como un átomo de cloro o bromo o un átomo de hidrógeno.

Es también preferido que X independientemente represente un enlace sencillo o un átomo de oxígeno o un grupo metileno, más preferentemente un enlace sencillo o un átomo de oxígeno y más preferentemente un átomo de oxígeno.

Ejemplos específicos de los derivados de 2-fenilpiran-4-ona de la presente invención incluyen:



R^3	R^d	R^a	R^b	R^c	R^d	R^e
Me	H	H	Br	H	H	H
Me	H	Br	H	H	H	H
Me	H	H	Me	H	H	H
Me	H	Me	H	H	H	H
Me	H	Me	H	F	H	H
Me	H	Me	H	Cl	H	H
Me	H	F	H	Me	H	H
Me	H	Cl	H	Me	H	H
Me	H	H	Me	F	H	H
Me	H	H	F	Me	H	H
Me	H	H	Cl	Me	H	H
Me	H	F	H	Br	H	H
Me	H	Cl	H	Br	H	H
Me	H	Br	H	Br	H	H
Me	Cl	H	H	H	H	H
Me	Cl	H	H	F	H	H
Me	Cl	H	F	H	H	H
Me	Cl	F	H	H	H	H
Me	Cl	H	H	Cl	H	H
Me	Cl	H	Cl	H	H	H
Me	Cl	Cl	H	H	H	H
Me	Cl	H	H	Br	H	H
Me	Cl	H	Br	H	H	H
Me	Cl	Br	H	H	H	H
Me	Cl	H	H	Me	H	H
Me	Cl	H	Me	H	H	H
Me	Cl	Me	H	H	H	H
Me	Cl	F	H	F	H	H
Me	Cl	F	H	H	F	H
Me	Cl	H	F	F	H	H
Me	Cl	F	H	H	H	F

95
45

Me	Cl	Cl	H	Cl	H	H
Me	Cl	Cl	H	H	Cl	H
Me	Cl	H	Cl	Cl	H	H
Me	Cl	Cl	H	H	H	Cl
Me	Cl	F	H	Cl	H	H
Me	Cl	Cl	H	F	H	H
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Me	Cl	H	Cl	F	H	H
Me	Cl	H	F	Cl	H	H
Me	Cl	F	H	Me	H	H
Me	Cl	Cl	H	Me	H	H
Me	Cl	Me	H	F	H	H
Me	Cl	Me	H	Cl	H	H
Me	Cl	H	Me	F	H	H
Me	Cl	H	Me	Cl	H	H
Me	Cl	H	F	Me	H	H
Me	Cl	H	Cl	Me	H	H
Me	Br	H	H	H	H	H
Me	Br	H	H	F	H	H
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Me	Br	F	H	H	H	H
Me	Br	H	H	Cl	H	H
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Me	Br	Cl	H	H	H	H
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Me	Br	H	Br	H	H	H
Me	Br	Br	H	H	H	H
Me	Br	H	H	Me	H	H
Me	Br	H	Me	H	H	H
Me	Br	Me	H	H	H	H
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Me	Br	F	H	Br	H	H
Me	Br	Br	H	F	H	H

96

96

Me	Br	H	Cl	F	H	H
Me	Br	H	F	Cl	H	H
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Me	Me	F	H	H	F	H
Me	Me	H	F	F	H	H
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Me	Me	Cl	H	Cl	H	H
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Me	Me	H	Cl	Cl	H	H
Me	Me	Cl	H	H	H	Cl
Me	Me	F	H	Cl	H	H
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Me	Me	F	H	Br	H	H
Me	Me	Br	H	F	H	H
Me	Me	H	Cl	F	H	H
Me	Me	H	F	Cl	H	H
Me	Me	F	H	Me	H	H
Me	Me	Cl	H	Me	H	H
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Me	Me	Me	H	Cl	H	H
Me	Me	H	Me	F	H	H
Me	Me	H	Me	Cl	H	H

Me	Me	H	F	Me	H	H
Me	Me	H	Cl	Me	H	H
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Me	$CH=CH_2$	Cl	H	H	H	Cl
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Me	$CH=CH_2$	F	H	Me	H	H
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Me	Et	H	Cl	H	H	H

98
AB

Me	Et	Cl	H	H	H	H
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Me	C≡CH	Br	H	H	H	H
Me	C≡CH	H	H	Me	H	H
Me	C≡CH	H	Me	H	H	H
Me	C≡CH	Me	H	H	H	H
Me	C≡CH	F	H	F	H	H

99
99

Me	C≡CH	F	H	H	F	H
Me	C≡CH	H	F	F	H	H
Me	C≡CH	F	H	H	H	F
Me	C≡CH	Cl	H	Cl	H	H
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Et	Me	F	H	Cl	H	H

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Pr	Et	H	Cl	Me	H	H
CH_2OH	H	H	H	H	H	H
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CH_2OH	H	H	F	Me	H	H
CH_2OH	H	H	Cl	Me	H	H
CH_2OCH_3	H	H	H	H	H	H
CH_2OCH_3	H	H	H	F	H	H
CH_2OCH_3	H	H	F	H	H	H

102
102

CH_2OCH_3	H	F	H	H	H	H
CH_2OCH_3	H	H	H	Cl	H	H
CH_2OCH_3	H	H	Cl	H	H	H
CH_2OCH_3	H	Cl	H	H	H	H
CH_2OCH_3	H	H	H	Br	H	H
CH_2OCH_3	H	H	Br	H	H	H
CH_2OCH_3	H	Br	H	H	H	H
CH_2OCH_3	H	H	H	Me	H	H
CH_2OCH_3	H	H	Me	H	H	H
CH_2OCH_3	H	Me	H	H	H	H
CH_2OCH_3	H	F	H	F	H	H
CH_2OCH_3	H	F	H	H	F	H
CH_2OCH_3	H	H	F	F	H	H
CH_2OCH_3	H	F	H	H	H	F
CH_2OCH_3	H	Cl	H	Cl	H	H
CH_2OCH_3	H	Cl	H	H	Cl	H
CH_2OCH_3	H	H	Cl	Cl	H	H
CH_2OCH_3	H	Cl	H	H	H	Cl
CH_2OCH_3	H	F	H	Cl	H	H
CH_2OCH_3	H	Cl	H	F	H	H
CH_2OCH_3	H	F	H	Br	H	H
CH_2OCH_3	H	Br	H	F	H	H
CH_2OCH_3	H	H	Cl	F	H	H
CH_2OCH_3	H	H	F	Cl	H	H
CH_2OCH_3	H	F	H	Me	H	H
CH_2OCH_3	H	Cl	H	Me	H	H
CH_2OCH_3	H	Me	H	F	H	H
CH_2OCH_3	H	Me	H	Cl	H	H
CH_2OCH_3	H	H	Me	F	H	H
CH_2OCH_3	H	H	Me	Cl	H	H
CH_2OCH_3	H	H	F	Me	H	H
CH_2OCH_3	H	H	Cl	Me	H	H
CF_2H	H	H	H	H	H	H
CF_2H	H	H	H	F	H	H
CF_2H	H	H	F	H	H	H
CF_2H	H	F	H	H	H	H
CF_2H	H	H	H	Cl	H	H
CF_2H	H	H	Cl	H	H	H
CF_2H	H	Cl	H	H	H	H
CF_2H	H	H	H	Br	H	H
CF_2H	H	H	Br	H	H	H
CF_2H	H	Br	H	H	H	H
CF_2H	H	H	H	Me	H	H

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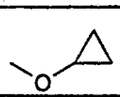
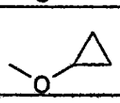
CF_2H	H	H	Me	H	H	H
CF_2H	H	Me	H	H	H	H
CF_2H	H	F	H	F	H	H
CF_2H	H	F	H	H	F	H
CF_2H	H	H	F	F	H	H
CF_2H	H	F	H	H	H	F
CF_2H	H	Cl	H	Cl	H	H
CF_2H	H	Cl	H	H	Cl	H
CF_2H	H	H	Cl	Cl	H	H
CF_2H	H	Cl	H	H	H	Cl
CF_2H	H	F	H	Cl	H	H
CF_2H	H	Cl	H	F	H	H
CF_2H	H	F	H	Br	H	H
CF_2H	H	Br	H	F	H	H
CF_2H	H	H	Cl	F	H	H
CF_2H	H	H	F	Cl	H	H
CF_2H	H	F	H	Me	H	H
CF_2H	H	Cl	H	Me	H	H
CF_2H	H	Me	H	F	H	H
CF_2H	H	Me	H	Cl	H	H
CF_2H	H	H	Me	F	H	H
CF_2H	H	H	Me	Cl	H	H
CF_2H	H	H	F	Me	H	H
CF_2H	H	H	Cl	Me	H	H
CF_2H	Br	F	H	F	H	H
CF_2H	Me	F	H	F	H	H
$CH_2OCH_2CH_3$	H	H	H	F	H	H
$CH_2OCH_2CH_3$	H	H	H	Cl	H	H
$CH_2OCH_2CH_3$	H	F	H	F	H	H
$CH_2OCH_2CH_2CH_3$	H	H	H	F	H	H
$CH_2OCH_2CH_2CH_3$	H	H	H	Cl	H	H
$CH_2OCH_2CH_2CH_3$	H	F	H	F	H	H
$CH_2OCH(CH_3)_2$	H	H	H	F	H	H
$CH_2OCH(CH_3)_2$	H	H	H	Cl	H	H
$CH_2OCH(CH_3)_2$	H	F	H	F	H	H
$CH_2OCH_2CH=CH_2$	H	H	H	F	H	H
$CH_2OCH_2CH=CH_2$	H	H	H	Cl	H	H
$CH_2OCH_2CH=CH_2$	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H

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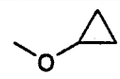
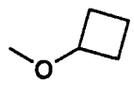
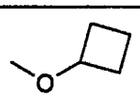
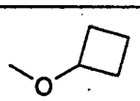
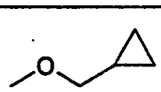
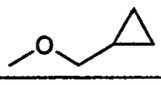
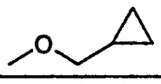
	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H
	H	F	H	F	H	H
	H	H	H	F	H	H
	H	H	H	Cl	H	H
	H	F	H	F	H	H
CH_2OCOCH_3	H	H	H	H	H	H
CH_2OCOCH_3	H	H	H	F	H	H
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CH_2OCOCH_3	H	F	H	H	H	H
CH_2OCOCH_3	H	H	H	Cl	H	H
CH_2OCOCH_3	H	H	Cl	H	H	H
CH_2OCOCH_3	H	Cl	H	H	H	H
CH_2OCOCH_3	H	H	H	Br	H	H
CH_2OCOCH_3	H	H	Br	H	H	H
CH_2OCOCH_3	H	Br	H	H	H	H
CH_2OCOCH_3	H	Me	H	H	H	H
CH_2OCOCH_3	H	F	H	F	H	H
CH_2OCOCH_3	H	F	H	H	F	H
CH_2OCOCH_3	H	H	F	F	H	H
CH_2OCOCH_3	H	F	H	H	H	F
CH_2OCOCH_3	H	Cl	H	Cl	H	H
CH_2OCOCH_3	H	Cl	H	H	Cl	H
CH_2OCOCH_3	H	H	Cl	Cl	H	H
CH_2OCOCH_3	H	Cl	H	H	H	Cl
CH_2OCOCH_3	H	F	H	Cl	H	H
CH_2OCOCH_3	H	Cl	H	F	H	H
CH_2OCOCH_3	H	F	H	Br	H	H
CH_2OCOCH_3	H	Br	H	F	H	H
CH_2OCOCH_3	H	H	Cl	F	H	H
CH_2OCOCH_3	H	H	F	Cl	H	H
CH_2OCOCH_3	H	Me	H	F	H	H

CH_2OCOCH_3	H	Me	H	Cl	H	H
COOH	H	H	H	H	H	H
COOH	H	H	H	F	H	H
COOH	H	H	F	H	H	H
COOH	H	F	H	H	H	H
COOH	H	H	H	Cl	H	H
COOH	H	H	Cl	H	H	H
COOH	H	Cl	H	H	H	H
COOH	H	H	H	Br	H	H
COOH	H	H	Br	H	H	H
COOH	H	Br	H	H	H	H
COOH	H	Me	H	H	H	H
COOH	H	F	H	F	H	H
COOH	H	F	H	H	F	H
COOH	H	H	F	F	H	H
COOH	H	F	H	H	H	F
COOH	H	Cl	H	Cl	H	H
COOH	H	Cl	H	H	Cl	H
COOH	H	H	Cl	Cl	H	H
COOH	H	Cl	H	H	H	Cl
COOH	H	F	H	Cl	H	H
COOH	H	Cl	H	F	H	H
COOH	H	F	H	Br	H	H
COOH	H	Br	H	F	H	H
COOH	H	H	Cl	F	H	H
COOH	H	H	F	Cl	H	H
COOH	H	Me	H	F	H	H
COOH	H	Me	H	Cl	H	H

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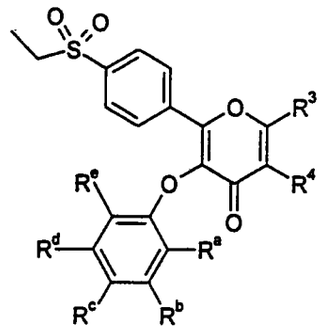

R^3	R^4	R^a	R^b	R^c	R^d	R^e
Me	H	F	H	F	H	H

y sales farmacéuticamente aceptables de los mismos.

Los compuestos específicos de especial interés son:

3-(4-fluoro-2-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(4-cloro-2-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(2-cloro-4-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(2-bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(3-bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(4-bromo-2-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(4-bromo-2-clorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(2,4-dibromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(2,4-difluorofenoxi)-2-(4-etansulfonilfenil)-6-metilpiran-4-ona;

2-(4-metansulfonilfenil)-6-metil-3-(2-metilfenoxi)piran-4-ona;

2-(4-metansulfonilfenil)-6-metil-3-(3-metilfenoxi)piran-4-ona;

3-(2-fluoro-4-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(2,4-difluorofenoxi)-6-etil-2-(4-metansulfonilfenil)-5-metil piran-4-ona;

3-cloro-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona;

3-cloro-5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-cloro-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-bromo-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona;

3-bromo-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-(2,4-difluorofenoxi)-5,6-dimetil-2-(4-metansulfonilfenil)piran-4-ona;

3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metil-5-vinil piran-4-ona;

3-(2,4-difluorofenoxi)-5-etil-2-(4-metansulfonilfenil)-6-metil piran-4-ona;

3-(2,4-difluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona;

3-(4-fluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona;

3-(4-clorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona;

3-(2-fluoro-4-bromofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona;

3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran -4-ona;

3-(4-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona;

3-(4-clorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona;

acetato de [5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

acetato de [5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

acetato de [5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

ácido 5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico;

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ácido 5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico;

6-(1,1-difluorometil)-3-(2,4-difluorofenoxi)-2-(4-metansulfonil fenil)piran-4-ona;

6-(1,1-difluorometil)-3-(4-bromofenoxi)-2-(4-metansulfonilfenil) piran-4-ona;

6-(1,1-difluorometil)-2-(4-metansulfonilfenil)-3-(4-metilfenoxi) piran-4-ona;

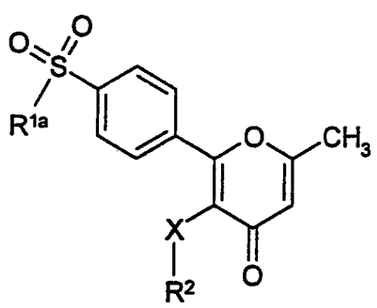
3-bromo-2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metan sulfonilfenil)piran-4-ona;

2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metansulfonil fenil)-3-metilpiran-4-ona;

y sales farmacéuticamente aceptables de los mismos.

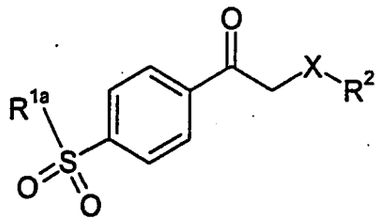
La presente invención se refiere también a procedimientos para la preparación de un compuesto de fórmula (I) el cual depende de la definición de R^3 y R^4. Cuando R^3 es un grupo alquilo y R^4 es un átomo de hidrógeno o un grupo alquilo, compuestos de fórmula (I) se preparan de acuerdo con la definición de R^1. Así, compuestos de fórmula (I) en que R^3 es un grupo metilo, R^4 es un átomo de hidrógeno y R^1 es un grupo alquilo o un grupo $-NR^5R^6$ en que R^5 y R^6 son grupos alquilo, es decir un derivado de 2-fenilpiran-4-ona de fórmula (II)

(II)



en donde R^{1a} es un grupo alquilo o un grupo $-NR^{5a}R^{6a}$ en que R^{5a} y R^{6a} cada uno independientemente son grupos alquilo, y R^2 y X son como se ha definido anteriormente, que comprende la reacción de un derivado carbonílico de fórmula (III):

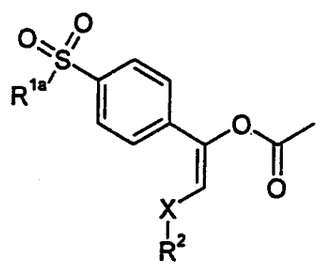
(III)



en donde R^{1a}, R^2 y X son como se ha definido anteriormente, con un exceso de ácido acético anhidro o anhídrido acético y ácido polifosfórico, a una temperatura desde 90°C hasta 150°C.

El compuesto de fórmula (II) se puede también preparar por reacción de un derivado vinílico de fórmula (IV):

(IV)

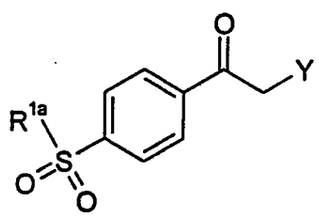


en donde R^{1a}, R^2 y X son como se ha definido anteriormente, con un exceso de anhídrido acético y ácido polifosfórico a una temperatura desde 80°C hasta 120°C.

El derivado vinílico de fórmula (IV) se puede obtener por reacción de un derivado carbonílico de fórmula (III) con anhídrido acético y ácido metansulfónico a una temperatura desde 50°C hasta 100°C.

El derivado carbonílico de fórmula (III) se puede obtener por métodos bien conocidos en la bibliografía (EP-A-714883; WO 96/06840; WO 96/31509 y DE-2064520) o cuando X representa un átomo de oxígeno o un átomo de azufre, por reacción de un derivado fenacilo de fórmula (V):

(V)



en donde R^{1a} es como se ha definido anteriormente e Y representa un

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átomo de cloro o bromo, con un derivado hidroxi o mercapto de fórmula (VI):

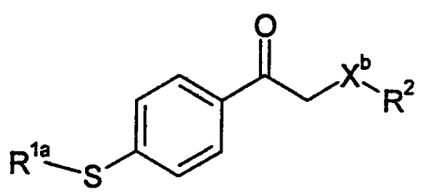
(VI) $HX^a - R^2$

en donde R^2 es como se ha definido anteriormente y X^a es un átomo de oxígeno o un átomo de azufre.

La reacción entre el derivado fenacilo de fórmula (V) y el alcohol o tiol de fórmula (VI) se puede llevar a cabo por calentamiento de una mezcla de estos dos productos de partida, opcionalmente en una mezcla de disolventes como cloruro de metileno, benceno o tolueno y agua, a una temperatura desde 15°C hasta 30°C y en presencia de un catalizador de transferencia de fase tal como cloruro de benciltrietilamonio.

El derivado carbonílico de fórmula (III) en que X es distinto de un átomo de azufre, también se puede preparar por reacción de un tioderivado de fórmula (VII):

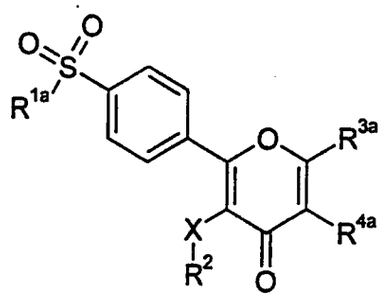
(VII)



en donde R^{1a} y R^2 son como se ha definido anteriormente, y X^b es un enlace sencillo, un átomo de oxígeno o un grupo metileno, con un agente oxidante, preferentemente monoperoxiftalato de magnesio o ácido 3-cloroperoxibenzoico. La reacción se lleva a cabo preferentemente en un disolvente orgánico tal como una mezcla de cloruro de metileno con metanol o etanol, a una temperatura desde 10°C hasta 40°C.

La presente invención también se refiere a un procedimiento para la preparación de un compuesto de fórmula (I) en donde R^3 y R^4 son grupos alquilo y R^1 es un grupo alquilo o un grupo $-NR^5R^6$ en que R^5 y R^6 son grupos alquilo, es decir un derivado 2-fenilpiran-4-ona de fórmula (VIII):

(VIII)



en donde R^{4a} es un grupo alquilo, R^{3a} representa un grupo CH_2-R^{4a} y R^{1a}, R^2 y X son como se ha definido anteriormenteare, que comprende la reacción de un derivado carbonílico de fórmula (III) con un exceso de un anhídrido de fórmula (IX):

(IX) $(R^{4a}CH_2CO)_2\ O$

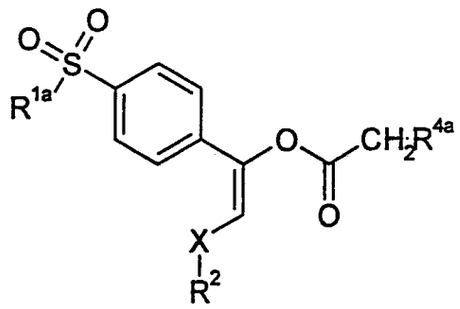
o un ácido carboxílico de fórmula (X):

(X) $R^{4a}CH_2COOH$

y ácido polifosfórico a una temperatura desde 90°C hasta 150°C.

El compuesto de fórmula (VIII) también se puede obtener por reacción de un derivado vinílico de fórmula (XI):

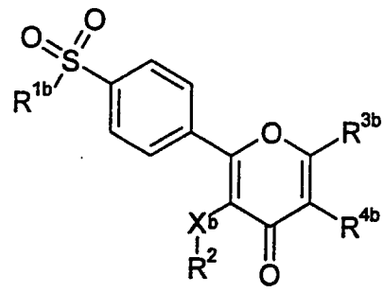
(XI)



en donde R^{1a}, R^2, R^{4a} y X son como se ha definido anteriormente con un exceso de un anhídrido de fórmula (IX) y ácido polifosfórico a una temperatura desde 90°C hasta 150°C. El vinil derivado de fórmula (XI) se puede preparar por reacción de un derivado carbonílico de fórmula (III) con un anhídrido de fórmula (IX) y ácido metansulfónico a una temperatura desde 50°C hasta 100°C.

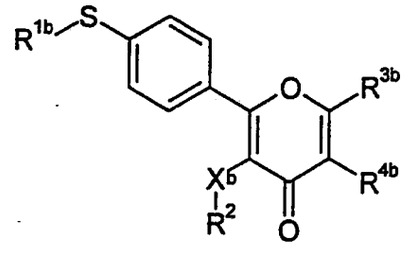
La presente invención también se refiere a un procedimiento para la preparación de un compuesto de fórmula (I) en donde R^3 es un grupo alquilo, R^4 es un átomo de hidrógeno o un grupo alquilo, R^1 es un grupo alquilo, y X es distinto de un átomo de azufre, es decir un derivado 2-fenilpiran-4-ona de fórmula (XII):

(XII)



en donde R^{1b} es un grupo alquilo, R^{3b} es un grupo metilo o un grupo $R^{4b}CH_2$, R^{4b} es un átomo de hidrógeno o un grupo alquilo y R^2 y X^b son como se ha definido anteriormente, por reacción de un mercapto derivado de fórmula (XIII):

(XIII)



en donde R^{1b}, R^{3b}, R^{4b}, R^2 y X^b son como se ha definido anteriormente con un agente oxidante, preferentemente con monoperoxiftalato de magnesio o ácido 3-cloroperoxibenzoico.

La reacción entre el mercapto derivado de fórmula (XIII) y el agente oxidante se lleva a cabo preferentemente, tal como se ha descrito anteriormente para el compuesto de fórmula (VII), en un disolvente orgánico tal como una mezcla de cloruro de metileno con metanol o etanol, a una temperatura desde 10°C hata 40°C.

La presente invención se refiere adicionalmente a un procedimiento para la preparación de un compuesto de fórmula (I) en donde R^1 es un grupo $-NR^5R^6$, R^3 es un grupo alquilo y R^4 es un átomo de hidrógeno o un grupo alquilo, es decir un derivado 2-fenilpiran-4-ona de fórmula (XIV):

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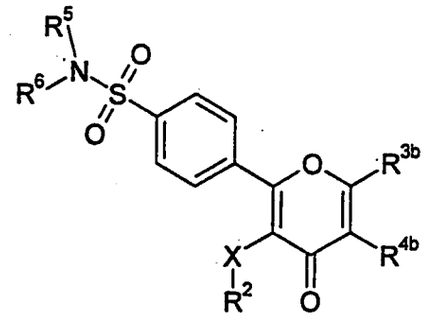
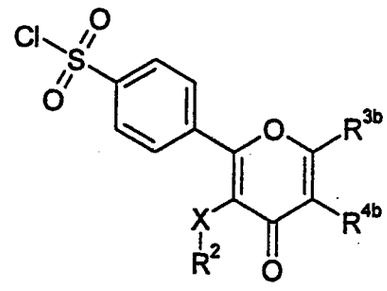
(XIV)



en donde R^2, R^{3b}, R^{4b}, R^5, R^6 y X son como se ha definido anteriormente por reacción de un clorosulfonil derivado de fórmula (XV):

(XV)



en donde R^2, R^{3b}, R^{4b} y X son como se ha definido anteriormente con una amina de fórmula (XVI):

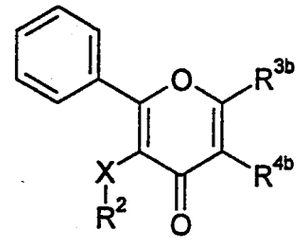
(XVI) R^5-NH-R^6

en donde R^5 y R^6 son como se ha definido anteriormente.

Esta reacción se lleva a cabo preferentemente a una temperatura desde 10°C hasta 40°C.

El clorosulfonil derivado de fórmula (XV) se prepara, por ejemplo, por reacción de un compuesto de fórmula (XVII):

(XVII)



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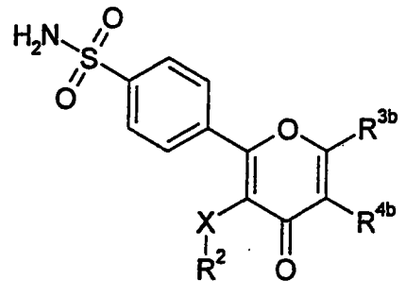
en donde R^2, R^{3b}, R^{4b} y X son como se ha definido anteriormente, con ácido clorosulfónico, preferentemente a una temperatura desde 80°C hasta 120°C.

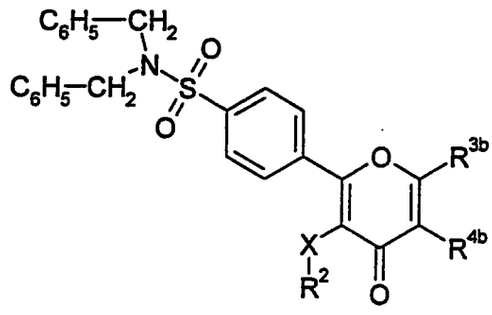
La presente invención se refiere también a un procedimiento para la preparación de un compuesto de fórmula (I) en donde R^3 es un grupo alquilo, R^4 es un átomo de hidrógeno o un grupo alquilo y R^1 es un grupo $-NR^5R^6$ en donde R^5 y R^6 son átomos de hidrógeno, es decir el derivado 2-fenilpiran-4-ona de fórmula (XVIII):

(XVIII)



en donde R^2, R^{3b}, R^{4b} y X son como se ha definido anteriormente por desbencilación del correspondiente derivado N,N-dibencilado de fórmula (XIX):

(XIX)



en donde R^2, R^{3b}, R^{4b} y X son como se ha definido anteriormente.

La desbencilación se lleva a cabo preferentemente con un exceso de ácido trifluoroacético, sulfúrico o metansulfónico a una temperatura desde 0°C hasta 120°C.

El intermedio de fórmula (XIX) se prepara de acuerdo con el procedimiento anterior utilizando los materiales de partida apropiados en donde R^5 y R^6 (o R^{5a} y R^{6a}) ambos representan grupos bencilo.

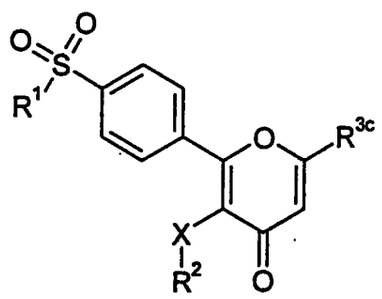
Los intermedios de fórmula (V) y (VII) utilizados en la preparación de los compuestos de la invención se preparan por

métodos descritos en la bibliografía, por ejemplo, en M.F. Saettone, J. Org. Chem. 31, p. 1959 (1966) and WO 96/06840.

Los compuestos intermedios de fórmula (XIII) y (XVII) se preparan por los mismos procedimientos descritos para la preparación de los compuestos de fórmula (II) y (VIII), con los materiales de partida apropiados.

Los derivados 2-fenilpiran-4-ona de fórmula (I) en donde R^3 es distinto de un grupo alquilo y R^4 es un átomo de hidrógeno, es decir derivados 2-fenilpiran-4-ona de fórmula (XX):

(XX)



en donde R^{3c} es un grupo hidroximetilo, alcoximetilo, C_3-C_7 cicloalcoximetilo, alquenilmetoximetilo, C_3-C_7 cicloalquil metoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo, difluorometilo, o un grupo CH_2OCOR^7, en donde R^7 es un grupo alquilo o un grupo fenilo, y R^1, X y R^2 son como se ha definido anteriormente, se preparan por procedimientos que estan representados en el siguiente esquema:

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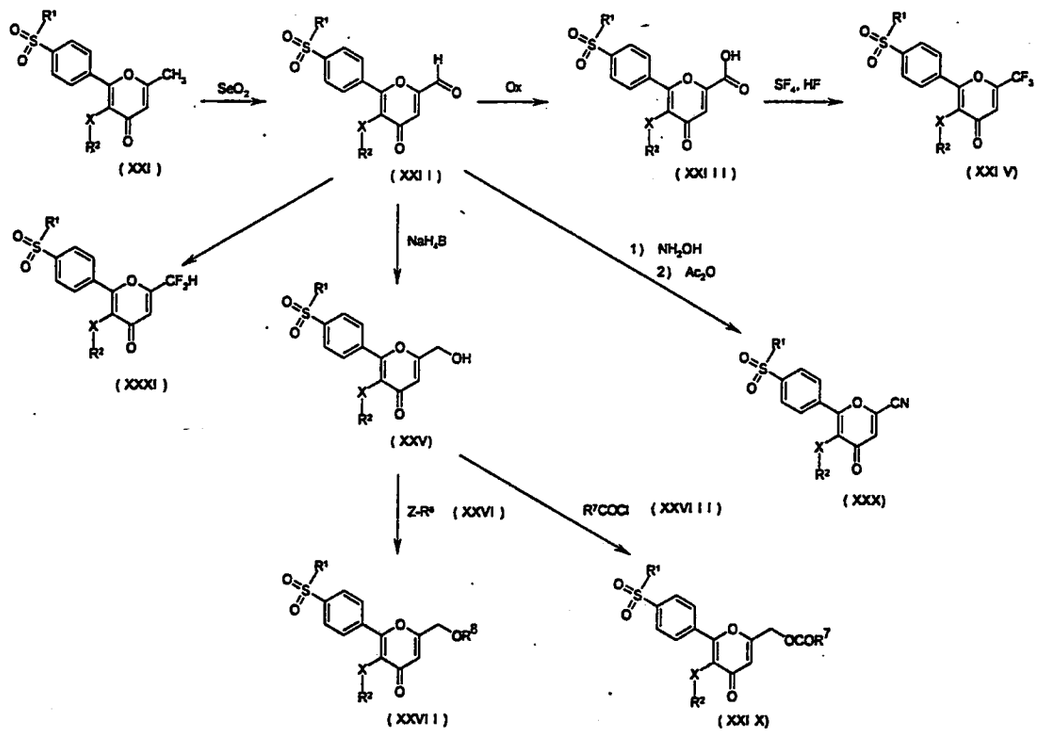


Como se puede ver en el esquema, los derivados 2-fenilpiran-4-ona de fórmula general (XX), se preparan a partir de compuestos de fórmula (I) en los cuales R^3 es un grupo metilo y R^4 es un átomo de hidrógeno, es decir compuestos de fórmula (XXI), cuyos procedimientos de preparación han sido descritos anteriormente. En una primera etapa, los compuestos de fórmula (XXI) se tratan con un agente oxidante como dióxido de selenio en un disolvente orgánico como tetrahidrofurano o dioxano, en un ractor a presión y a una temperatura desde 100°C hasta 190°C. Se obtiene el correspondiente aldehído de fórmula (XXII), el cual se usa como producto de partida para obtener los compuestos de fórmula general (XX).

Los compuestos de fórmula (XX) en donde R^{3c} es un grupo hidroxicarbonilo, es decir compuestos de fórmula (XXIII), se preparan a partir del correspondiente aldehído (XXII) por reacción con un agente oxidante como dicromato de piridinio u óxido de cromo (IV) en un disolvente orgánico tal como N,N-dimetilformamida, etanol o acetona/ácido sulfúrico, a una temparatura desde -5°C y 35°C. Los compuestos obtenidos (XXIII) se

utilizan como productos de partida para obtener los compuestos de fórmula (I) en donde R^{3c} es un grupo trifluorometilo, es decir compuestos de fórmula (XXIV). La reacción se lleva a cabo por reacción de compuestos (XXIII) con una mezcla de tetrafluoruro de azufre y fluoruro de hidrógeno, opcionalmente en presencia de un disolvente orgánico como cloruro de metileno, en un reactor a presión, y a una temperatura desde 20°C hasta 140°C.

Los compuestos de fórmula (XX) en donde R^{3c} representa un grupo hidroximetilo, es decir compuestos de fórmula (XXV) se preparan por reducción de los compuestos de fórmula (XXII) con hidruro de boro o aluminio anhidro, preferentemente con hidruro de boro y sodio en un disolvente como metanol o etanol y a una temperatura desde 10°C hasta 40°C. Una reacción posterior de los compuestos de fórmula (XXV) con un haluro apropiado de fórmula (XXVI):

(XXVI) $Z - R^8$

en donde Z representa un átomo de cloro, bromo o yodo y R^8 representa un grupo alquilo, C_3-C_7 cicloalquilo, alquenilmetilo, C_3-C_7 cicloalquilmetilo, o bencilo, proporciona los compuestos de fórmula (XX) en donde R^{3c} es un grupo alcoximetilo, C_3-C_7 cicloalcoximetilo, alquenilmetoximetilo, C_3-C_7 cicloalquilmetoxi metilo o benciloximetilo, es decir compuestos de fórmula (XXVII). La reacción se lleva a cabo en un disolvente orgánico como acetona, N,N-dimetilformamida o tetrahidrofurano en presencia de hidruro o amiduro de sodio o potasio, a una temperatura desde 20°C y 120°C.

Además, la reacción de compuestos de fórmula (XXV) con un apropiado haluro de acilo de fórmula (XXVIII):

(XXVIII) R^7COCl

en donde R^7 representa un grupo alquilo o un grupo fenilo proporciona compuestos de fórmula (XXIX). La reacción se lleva a cabo en un disolvente orgánico tal como tetrahidrofurano, cloruro de metileno, cloroformo o dioxano en presencia de una amina

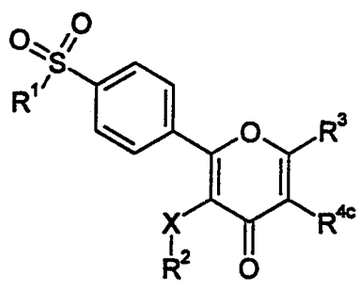
terciaria, tal como trietilamina, a una temperatura desde 20°C hasta la temperatura de ebullición del disolvente.

También los aldehídos de fórmula (XXII) se utilizan como productos de partida para obtener compuestos de fórmula (XX) en donde R^{3c} es un grupo nitrilo, es decir compuestos de fórmula (XXX). La reacción se lleva a cabo en una primera etapa por tratamiento de los aldehídos (XXII) con clorhidrato de hidroxilamina y ácido fórmico a una temperatura desde 80°C hasta 120°C. El derivado oxima resultante se aisla y se calienta con un exceso de anhídrido acético a una temperatura entre 100°C a 180°C.

Los compuestos de fórmula (XX) en donde R^{3c} representa un grupo difluorometilo, es decir compuestos de fórmula (XXXI), se preparan a partir de aldehídos de fórmula (XXII) por reacción con un reactivo fluorado como trifluoruro de dietilaminoazufre o una mezcla de tetrafluoruro de azufre-fluoruro de hidrógeno, opcionalmente en presencia de un disolvente orgánico como cloruro de metileno, benceno o tolueno y a una temperatura desde 0°C hasta 130°C.

La presente invención también proporciona un procedimiento para la preparación de compuestos de fórmula (I) en donde R^4 es diferente a un átomo de hidrógeno, es decir derivados 2-fenilpiran-4-ona de fórmula (XXXII):

(XXXII)



en donde R^{4c} es un grupo alquilo, alquenilo o alquinilo y R^1, R^2, R^3 y X son como se ha definido anteriormente, que comprende la reacción de un compuesto de fórmula (XXXIII):

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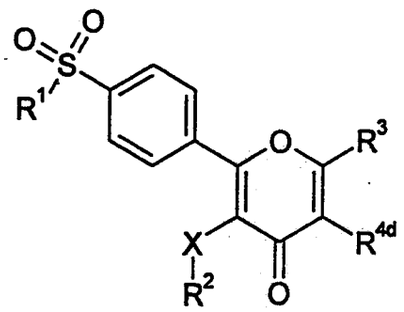
(XXXIII)



en donde R^{4d} es un átomo de cloro, bromo o yodo, preferentemente un átomo de bromo y R^1, R^2, R^3 y X son como se ha definido anteriormente, con un derivado de estaño de fórmula (XXXIV):

(XXXIV) $R^{4c}\ Sn\ (R^9)_3$

en donde R^{4c} es como se ha definido anteriormente y R^9 es un grupo alquilo. La reacción se lleva a cabo en un disolvente tal como dimetilformamida, tetrahidrofurano o dioxano, en presencia de una amina terciaria, tal como trietilamina, con tri-o-tolilfosfina y acetato de paladio (II), y a una temperatura desde 20°C hasta 150°C.

Los derivados de fórmula (XXXIII), en donde R^{4d} es preferentemente un átomo de bromo, se obtienen por reacción de un derivado de fórmula (XX) o un derivado de fórmula (XXI) con bromo o tribromuro de piridina, en un disolvente orgánico tal como 1,1,2,2-tetracloroetano, cloruro de metileno o cloroformo, en un reactor a presión, y a una temperatura desde 20°C hasta 180°C.

Los derivados 2-fenilpiran-4-ona de fórmula (I) en los cuales existe la presencia de un grupo básico, se pueden transformar por métodos conocidos, en sales farmacéuticamente aceptables, preferentemente sales de adición acida por tratamiento con un ácido orgánico o inorgánico como fumárico, tartárico, succínico o clorhídrico. También, los derivados de 2-fenilpiran-4-ona de fórmula (I) en los cuales R^3 representa un grupo hidroxicarbonilo, puden ser transformados en sales farmacológicamente aceptables con, por ejemplo, metales alcalinos como sodio o potasio por reacción con un hidróxido de metal alcalino.

El siguiente test biológico y resultados ilustran la siguiente invención.

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Actividad COX-1 y COX-2 en sangre total humana

La sangre recién extraída de voluntarios sanos quienes no habían tomado ningún fármaco antiinflamatorio no esteroidal durante al menos 7 días antes de la extracción de la sangre, se recogió en tubos que contenían heparina sódica (20 unidades/ml). Para la determinación de actividad COX-1, alícuotas de 500 µl de sangre se incubaron bien con 5 µl de vehículo (dimetilsulfóxido) o 5 µl de un compuesto a ensayar durante 1 hora a 37°C. El ionóforo de calcio A23187 (25 µM) se añade 20 minutos antes de finalizar la incubación. El plasma se separa por centrifugación (10 min. a 13000 rpm) y se mantiene a -30°C hasta que los niveles de TXB_2 se miden utilizando un inmunoensayo en fase sólida (ELISA).

El efecto de los compuestos se evalúa por incubación de cada compuesto a cinco/seis diferentes concentraciones con determinaciones por triplicado. Los valores CI_{50} se obtienen por regresión no-lineal utilizando InPlot, software GraphPad en un ordenador IBM.

Para la determinación de actividad COX-2, se incuban alícuotas de 500 µl de sangre en presencia de LPS (10 µg/ml) durante 24 horas a 37°C con objeto de inducir la expresión COX-2 (Patriagnani et al., J. Pharm. Exper. Ther. 271; 1705-1712 (1994)). El plasma se separa por centrifugación (10 min. a 13000 rpm) y se mantiene a -30°C hasta que los niveles de PGE_2 se miden utilizando un inmunoensayo en fase sólida (ELISA). Los efectos de los inhibidores se estudian por incubación de cada compuesto (5 µl alícuotas) a cinco/seis concentraciones diferentes con determinaciones por triplicado en presencia de LPS durante 24 horas. Los valores CI_{50} se obtienen por regresión no lineal utilizando InPlot, software GraphPad en un ordenador IBM.

Los resultados obtenidos de los ensayos biológicos se presentan en la Tabla 1.

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TABLA 1: Inhibición COX-1 y COX-2

Ejemplo	COX-1 CI_{50} (µM)	COX-2 CI_{50} (µM)	Relación COX-1/COX-2
1	21.2	0.18	118
2	38.5	0.13	296
3	16.3	0.24	68
6	40.2	0.15	268
7	33.4	0.21	159
8	57.5	1.13	51
10	19.9	0.086	231
11	14.2	0.30	47
16	26.0	0.53	74
17	20.0	0.78	27
18	76.7	0.82	93
19	14.6	0.082	178
20	31.2	1.43	22
21	35.6	0.58	62
22	53.0	0.19	279
23	2% at 100 µM	1.44	>70
24	13% at 100 µM	0.60	>150
26	21.1	0.17	124
27	86.3	0.32	270
28	91.9	0.44	209
30	50.3	0.14	359
31	17% at 100 µM	1.10	>90
32	450	0.42	1070
36	28.5	0.097	294
Indomethacin	0.19	0.22	0.86

Indometacina es el ácido 1-(4-clorobenzoil)-5-metoxi-2-metilindol-3-acético.

Como se observa en la Tabla 1, los derivados de 2-fenilpiran-4-ona de fórmula (I) son inhibidores potentes y selectivos de COX-2 mientras que el compuesto de referencia indometacina, es equipotente como inhibidor de COX-2 y COX-1. Así los compuestos de la invención son preferentemente inhibidores selectivos de COX-2 de mamíferos, por ejemplo COX-2 humana. Los compuestos de la

invención también tienen preferentemente una actividad inhibitoria baja hacia la COX-1 de mamíferos, por ejemplo COX-1 humana. La actividad inhibitoria puede ser medida típicamente por ensayos *in vitro*, por ejemplo como el que se describe anteriormente.

Los compuestos preferidos de la invención tienen un valor de CI_{50} para COX-2 inferior a 5 μM, preferentemente inferior a 3, más preferentemente inferior a 2.5 μM. Los compuestos preferidos de la invención también tienen un valor CI_{50} para COX-1 superior a 10 μM, preferentemente superior a 20 μM. Como un indicador de la selectividad para la inhibición de COX-2 sobre COX-1, la relación de COX-1/COX-2 en valores de CI_{50} es preferentemente superior a 20, 30 o 50, más preferentemente superior a 60, 100 o 200.

La presente invención se refiere también a un compuesto de fórmula (I) para uso en un método de tratamiento terapéutico humano o animal, en particular para el tratamiento del dolor, fiebre o inflamación, para inhibir la contracción de la musculatura lisa inducida por prostanoides, o para la prevención o tratamiento del cáncer colorectal o enfermedades neurodegenerativas, por ejemplo la enfermedad de Alzheimer.

La presente invención se refiere también al uso de un compuesto de fórmula (I) en la fabricación de un medicamento para el tratamiento del dolor, fiebre o inflamación, para inhibir la contracción de la musculatura lisa inducida por prostanoides o para la prevención del cáncer colorectal.

Los compuestos de fórmula (I) son útiles para aliviar el dolor, fiebre e inflamación de una variedad de trastornos entre los que se incluyen fiebre reumática, síntomas asociados con el resfriado u otras infecciones virales, resfriado común, dolor de espalda y cuello, dismenorrea, dolor de cabeza, dolor dental, torceduras y estiramientos, miositis, neuralgia, sinovitis, bursitis, tendinitis, heridas, después de actos quirúrgicos y extracciones dentales y artritis incluyendo artritis reumatoide, osteoartritis, gota, espondiloartropatías, lupus eritematoso y artritis juvenil. También pueden utilizarse en el tratamiento de trastornos inflamatorios de la piel como psoriasis, eczema, quemaduras y dermatitis. Además, tales compuestos se pueden usar para la prevención o tratamiento de cáncer colorectal o

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enfermedades neurodegenerativas, por ejemplo, la enfermedad de Alzheimer.

Los compuestos de fórmula (I) también inhiben la contracción de la musculatura lisa inducida por prostanoides y, por lo tanto, se pueden utilizar en el tratamiento de dismenorrea, parto prematuro, asma y bronquitis.

Los compuestos de fórmula (I) se pueden utilizar como alternativa a los fármacos antiinflamatorios no esteroidales, particularmente en aquellos casos en que los fármacos antiinflamatorios no esteroidales están contraindicados, como en el tratamiento de pacientes con trastornos gastrointestinales que incluyen úlcera péptica, gastritis, enteritis, colitis ulcerosa, diverticulitis, enfermedad de Crohn, síndrome intestinal inflamatorio y síndrome intestinal irritable, hemorragia gastrointestinal y trastornos de la coagulación, enfermedad renal (función renal disminuida), o aquellas previas a la cirugía o tratamientos con anticoagulantes, y aquellas susceptibles al asma inducida por fármacos antiinflamatorios no esteroidales.

Los compuestos pueden utilizarse también en el tratamiento de la inflamación en enfermedades vasculares, migraña, periarteritis nudosa, tiroiditis, anemia aplástica, enfermedad de Hodgkin, escleroderma, diabetes tipo I, miastenia gravis, sarcoidosis, síndrome nefrítico, síndrome de Behcet, polimiositis, hipersensibilidad, conjuntivitis, gingivitis e isquemia de miocardio.

Los compuestos de la presente invención son inhibidores del enzima ciclooxigenasa-2 y, por lo tanto, son útiles en el tratamiento de aquellas enfermedades mediadas por la ciclooxigenasa-2 citadas anteriormente.

Según esto, los derivados de 2-fenilpiran-4-ona de fórmula (I) y sales farmacéuticamente aceptables de los mismos, y composiciones farmacéuticas conteniendo tales compuestos y/o sales de los mismos, se pueden usar en un método de tratamiento de trastornos del cuerpo humano los cuales comprenden la administración al paciente que requiere de tal tratamiento de una cantidad efectiva de un derivado de 2-fenilpiran-4-ona de fórmula (I) o una sal farmacéuticamente aceptable del mismo.

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La presente invención también se refiere a composiciones farmacéuticas que comprenden, como un ingrediente activo, al menos un derivado de 2-fenilpiran-4-ona de fórmula (I) o una sal farmacológicamente aceptable del mismo en asociación con un excipiente farmacéuticamente aceptable o un diluyente. El ingrediente activo puede comprender del 0,001% al 99% en peso, preferentemente del 0,01% al 90% en peso de una composición dependiendo de la naturaleza de la formulación y si posteriormente se tiene que efectuar alguna dilución antes de su aplicación.

Preferentemente las composiciones se completan en una forma apropiada para la administración oral, tópica, nasal, inhalación, rectal, percutánea o inyectable.

Los excipientes farmacéuticamente aceptables que se mezclan con el compuesto activo, o sales de tal compuesto, para formar las composiciones de esta invención son bien conocidos en la bibliografía y los excipientes reales utilizados dependen del método de administración de las composiciones que se pretendan.

Las composiciones de esta invención se adaptan preferentemente para la administración inyectable u oral. En este caso, las composiciones para la administración oral pueden tomar la forma de comprimidos, comprimidos retard, comprimidos sublinguales, cápsulas o preparaciones líquidas, como mezclas, elixires, jarabes o suspensiones, conteniendo todas ellas el compuesto de la invención; tales preparaciones se realizan con los métodos bien conocidos en la bibliografía.

Los diluyentes que se pueden utilizar en la preparación de las composiciones incluyen diluyentes líquidos y sólidos los cuales son compatibles con el ingrediente activo, junto con agentes colorantes o saborizantes, si se desea. Los comprimidos o cápsulas pueden contener convenientemente entre 2 y 500 mg de ingrediente activo o la cantidad equivalente de una sal del mismo.

Las composiciones líquidas adaptadas para el uso oral pueden estar en forma de soluciones o suspensiones. Las soluciones pueden ser acuosas de una sal u otro derivado del compuesto activo en asociación con, por ejemplo, sacarosa para formar un jarabe. Las suspensiones pueden comprender un compuesto activo insoluble de la invención o una sal farmacéuticamente aceptable del mismo en

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asociación con agua, junto con un agente emulsionante o saborizante.

Las composiciones para inyección parenteral se preparan a partir de sales solubles, las cuales pueden o no estar liofilizadas y las cuales se pueden disolver en medios acuosos libres de pirógenos u otros fluídos apropiados para la inyección parenteral.

Las dosis efectivas están normalmente en el intervalo de 10 a 600 mg de ingrediente activo por día. La dosis diaria se puede administrar en uno o varios tratamientos, preferentemente de 1 a 4 tratamientos, por día.

La invención se ilustra con los siguientes ejemplos, los cuales no limitan el objeto de la invención de ninguna forma.

PREPARACIÓN 1

2-(2,4-Difluorofenoxi)-1-(4-metansulfonilfenil)etanona

a) A una solución de 2,4-difluorofenol (3,71 g; 29 mmol) y 2-bromo-1-(4-metilsulfanilfenil)etanona (7,00 g; 29 mmol) en cloruro de metileno (50 ml) se añade una solución de carbonato potásico (5,91 g; 43 mmol) y tetrabutilamonio hidrogenosulfato (0,48 g; 1.4 mmol) en agua (20 ml). La mezcla se agita a temperatura ambiente durante 16 horas. Se añade agua (100 ml), se decanta la fase orgánica, y la fase acuosa se extrae con cloruro de metileno (2 x 100 ml). La solución orgánica se seca (Na_2SO_4) y el disolvente se elimina a presión reducida. El sólido resultante se lava con eter etílico. Se obtiene 2-(2,4-difluorofenoxi) -1-(4-metilsulfanilfenil)etanona (6,60 g, 76%) como un sólido blanquecino.

b) Una solución del 80% de monoperoxiftalato de magnesio hexahidratado (15,26 g; 25 mmol) en agua (20 ml) se añade a una solución del compuesto anterior (6,60 g; 22 mmol) en cloruro de metileno (100 ml). La mezcla se agita a temperatura ambiente durante 16 horas. La reacción se vierte sobre una solución saturada de bicarbonato sódico (200 ml) y se extrae con cloruro de metileno (3 x 100 ml). La fase orgánica se seca (Na_2SO_4) y el disolvente se elimina a presión reducida. Se obtiene

2-(2,4-difluorofenoxi)-1-(4-metansulfonilfenil)etanona (4,97 g, 89%) en forma de un sólido blanquecino.

δ (DMSO): 3.31 (s, 3H), 5.72 (s, 2H), 6.93-7.05 (m, 1H), 7.15-7.36 (m, 2H), 8.12 (d, J=8.5 Hz, 2H), 8.22 (d, J=8.5 Hz, 2H).

PREPARACIÓN 2

2-(4-Fluorofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (72% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-fluorofenol según el procedimiento descrito en la Preparación 1.

δ (DMSO): 3.32 (s, 3H), 5.62 (s, 2H), 7.01-7.04 (m, 2H), 7.05-7.17 (m, 2H), 8.13 (d, J=8.0 Hz, 2H), 8.25 (d, J=8.0 Hz, 2H).

PREPARACIÓN 3

2-(4-Clorofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (89% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-clorofenol según el precedimiento descrito en la Preparación 1.

δ (DMSO): 3.30 (s, 3H), 5.65 (s, 2H), 7.03 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 8.12 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.5 Hz, 2H).

PREPARACIÓN 4

2-(4-Fluoro-2-metilfenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (75% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-fluoro-2-metilfenol según el procedimiento descrito en la Preparación 1.

δ (DMSO): 2.22 (s, 3H), 3.30 (s, 3H), 5.63 (s, 2H), 6.89-7.06 (m, 3H), 8.08 (d, J=8.0 Hz, 2H), 8.21 (d, J=8.0 Hz, 2H)

PREPARACIÓN 5

2-(4-Cloro-2-metilfenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (77% rendimiento total) a patir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-cloro-2-metilfenol según el procedimiento descrito en la Preparación 1.

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δ (DMSO): 2.23 (s, 3H), 3.31 (s, 3H), 5.68 (s, 2H), 6.96 (d 127
J=8.5 Hz, 1H), 7.15 (d, J=8.5 Hz, 1H), 7.25 (s, 1H), 8.12 (d, J=8.5 Hz, 2H), 8.24 (d, J=8.5 Hz, 2H).

PREPARACIÓN 6

2-(2-Cloro-4-metilfenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (84% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 2-cloro-4-metilfenol seún el procedimiento descrito en la Preparación 1.

δ (DMSO): 2.23 (s, 1H), 3.32 (s, 3H), 5.74 (s, 2H), 7.02-7.04 (m, 2H), 7.24 (s, H), 8.12 (d, J=8.1 Hz, 2H), 8.22 (d, J=8.1 Hz, 2H).

PREPARACIÓN 7

2-(2-Bromofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (72% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 2-bromofenol según el procedimiento descrito en la Preparación 1.

δ ($CDCl_3$):3.07 (s, 3H), 5.30 (s, 2H), 6.80-6.94 (m, 2H), 7.20-7.26 (m, 1H), 7.53 (d, J=7.5 Hz, 1H), 8.08 (d, J=9.0 Hz, 2H), 8.23 (d, J=9.0 Hz, 2H).

PREPARACIÓN 8

2-(3-Bromofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (57% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 3-bromofenol según el procedimiento descrito en la Preparación 1.

δ (DMSO):3.33 (s, 3H), 5.72 (s, 2H), 7.03-7.06 (m, 1H), 7.17 (d, J=8.0 Hz, 1H), 7.25 (d, J=8.0 Hz, 1H), 7.32 (s, 1H), 8.13 (d, J=8.0 Hz, 2H), 8.24 (d, J=8.0 Hz, 2H).

PREPARACIÓN 9

2-(4-Bromofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (81% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-bromofenol según el procedimiento descrito en la Preparación 1.

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δ ($CDCl_3$): 3.33 (s, 3H), 5.66 (s, 2H), 7.00(d, J=9.0 Hz, 2H), 7.46 (d, J=9.0 Hz, 2H), 8.12 (d, J=9.0 Hz, 2H), 8.24 (d, J=9.0 Hz, 2H). 128

PREPARACIÓN 10

2-(4-Bromo-2-fluorofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (78% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-bromo-2-fluorofenol según el procedimiento descrito en la Preparación 1.

δ (DMSO): 3.32 (s, 3H), 5.80 (s, 2H), 7.08-7.38 (m, 2H), 7.6 (d,J=8.0 Hz, 1H), 8.13 (d, J=8.0 Hz, 2H), 8.24 (d, J=8,Hz, 2H)

PREPARACIÓN 11

2-(4-Bromo-2-clorofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (68% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 4-bromo-2-clorofenol según el procedimiento descrito en la Preparación 1.

δ ($CDCl_3$): 3.13 (s, 3H), 5.32 (s, 2H), 6.77 (d, J=9.0 Hz, 1H), 7.32 (d, J=9.0 Hz, 1H), 7.56 (s, 1H), 8.12 (d, J=7.5 Hz, 2H), 8.24 (d, J=7.5 Hz, 2H).

PREPARACIÓN 12

2-(2,4-Dibromofenoxi)-1-(4-metansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (85% rendimiento total) a partir de 2-bromo-1-(4-metilsulfanilfenil)etanona y 2,4-dibromofenol según el procedimiento descrito en la Preparación 1.

δ ($CDCl_3$): 3.09 (s, 3H), 5.31 (s, 2H), 6.73 (d, J=9.0 Hz, 1H), 7.36 (d, J=9.0 Hz, 1H), 7.69 (s, 1H), 8.08 (d, J=7.5 Hz, 2H), 8.23 (d, J=7.5 Hz, 2H).

PREPARACIÓN 13

2-(2,4-Difluorofenoxi)-1-(4-etansulfonilfenil)etanona

Se obtiene en forma de un sólido blanquecino (69% rendimiento total) a partir de 2-bromo-1-(4-etilsulfanilfenil)etanona y 2,4-difluorofenol según el procedimiento descrito en la Preparación 1.

δ ($CDCl_3$): 1.31 (t, J=9.0 Hz, 3H), 3.15 (q, J=9.0 Hz, 2H), 5.31 (s, 2H), 6.70-7.03 (m, 3H), 8.03 (d, J=8.0 Hz, 2H), 8.20 (d, J=8.0 Hz, 2H).

PREPARACIÓN 14

3-(4-Fluorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

El compuesto obtenido en la Preparación 2(0,75 g, 2,43 mmol) se añade a una suspensión de ácido polifosfórico (7,5 g) en ácido acético (11 ml), se calienta previamente 95-100°C. La mezcla se calienta a 140°C durante 4 horas y se deja enfriar. A continuación la reacción se vierte sobre agua-hielo, se extrae con acetato de etilo (2 x 100 ml), la solución orgánica se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El aceite residual se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:1) como eluyente. Se obtiene 3-(4-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona (0,26 g, 11%) en forma de un sólido blanquecino.

δ (DMSO): 2.40 (s, 3H), 3.27 (s, 3H), 6.42 (s, 1H), 6.94-7.04 (m, 2H), 7.06-7.14 (m, 2H), 8.04 (s, 4H).

PREPARACIÓN 15

3-(4-Bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-one

Se obtiene en forma de un sólido blanquecino (19% rendimiento total) a partir del compuesto de referencia de la Preparación 9 y ácido acético según el procedimiento descrito en la Preparación 14.

δ ($CDCl_3$): 2.44 (s, 3H), 3.06 (s, 3H), 6.36 (s, 1H) 6.89 (d, J=9.0 Hz, 2H), 7.20 (d, J=9.0 Hz, 2H), 8.00 (d, J=9.0 Hz, 2H), 8.07 (d, J=9.0 Hz, 2H).

PREPARACIÓN 16

Acetato de 2-(2,4-difluorofenoxi)-1-(4-metansulfonilfenil)vinilo

Acido metansulfónico (7,41 g, 77 mmol) se añade a una mezcla del compuesto obtenido en la Preparación 1 (10,0 g, 30,7 mmol) y anhídrido acético (20,0 g, 0,196 mol), calentada previamente a 80°C. Después de 2 horas, la reacción se enfría y se añade agua (50 ml) lentamente, manteniendo la temperatura por debajo de 30°C.

Se obtiene en forma de un sólido blanquecino (28%) a partir del compuesto obtenido en la Preparación 6 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 159°C

δ (DMSO): 2.23 (s, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 6.48 (s, 1H), 6.81 (d, J=8.7 Hz, 1H), 6.98 (d, J=8.7 Hz, 1H), 7.32 (s, 1H), 8.07 (s, 4H).

EJEMPLO 4

3-(2-Bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (32%) a partir del compuesto obtenido en la Preparación 7 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 197-199°C

δ ($CDCl_3$): 2.46 (s, 3H), 3.11 (s, 3H), 6.43 (s, 1H), 6.67 (d, J=7.5 Hz, 1H), 6.92 (t, J=7.5 Hz, 1H), 7.18 (t, J=7.5 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 8.04 (d, J=9.0 Hz, 2H), 8.18 (d, J=9.0 Hz, 2H).

EJEMPLO 5

3-(3-Bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (15%) a partir del compuesto obtenido en la Preparación 8 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

LRMS: m/z 434 $(M+1)^+$.

δ ($CDCl_3$): 2.45 (s, 3H), 3.09 (s, 3H), 6.40 (s, 1H), 6.91-6.93 (m, 1H), 7.08 (s, 1H), 7.15-7.20 (m, 2H), 8.03 (d, J=8.5 Hz, 2H), 8.07 (d, J=8.5 Hz, 2H).

EJEMPLO 6

3-(4-Bromo-2-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (31%) a partir del compuesto obtenido en la Preparación 10 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 215°C

δ ($CDCl_3$): 2.45 (s, 3H), 3.08 (s, 3H), 6.34 (s, 1H), 6.74 (t, J=9.0 Hz, 1H), 7.12 (d, J=9.0 Hz, 1H), 7.29 (d, J=9.0 Hz, 1H), 8.04 (d, J=9.0 Hz, 2H), 8.10 (d, J=9.0 Hz, 2H).

EJEMPLO 7

3-(4-Bromo-2-clorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (43%) a partir del compuesto obtenido en la Preparación 11 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 214-215°C

δ ($CDCl_3$): 2.47 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.58 (d, J=8.5 Hz, 1H), 7.20 (d, J=8.5 Hz, 1H), 7.56 (s, 1H), 8.03 (d, J=7.5 Hz, 2H), 8.12 (d, J=7.5 Hz, 2H).

EJEMPLO 8

3-(2,4-Dibromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (17%) a partir del compuesto obtenido en la Preparación 12 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 231°C

δ ($CDCl_3$): 2.46 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.55 (d, J=9.0 Hz, 1H), 7.25 (d, J=9.0 Hz, 1H), 7.73 (s, 1H), 8.03 (d, J=7.5 Hz, 2H), 8.13 (d, J=7.5 Hz, 2H).

EJEMPLO 9

3-(2,4-Difluorofenoxi)-2-(4-etansulfonilfenil)-6-metilpiran-4-ona

Se obtiene en forma de un sólido blanquecino (18%) a partir del compuesto obtenido en la Preparación 13 y anhídrido acético según el procedimiento descrito en el Ejemplo 1.

p.f.: 154-155°C

δ ($CDCl_3$): 1.30 (t, J=7.5 Hz, 3H), 2.45 (s, 3H), 3.15 (q, J=7.5 Hz, 2H), 6.33 (s, 1H), 6.69-6.76 (m, 1H), 6.81-6.93 (m, 2H), 8.00 (d, J=8.7 Hz, 2H), 8.12 (d, J=8.7 Hz, 2H)

EJEMPLO 10

2-(4-Metansulfonilfenil)-6-metil-3-(2-metilfenoxi)piran-4-ona

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A una solución del compuesto obtenido en el Ejemplo 4 (1,40 g, 3,21 mmol) en dimetilformamida (16 ml) se añaden tetrametilestaño (2,40 ml, 17,3 mmol), tri-o-tolilfosfina (0,23 g, 0,77 mmol), acetato de paladio (0,043 g, 0,19 mmol) y trietilamina (1,45 ml, 10,3 mmol). La mezcla se calienta a 105°C durante 90 horas. Después de enfriar, el crudo se filtra a través de Celite® y el disolvente se elimina a presión reducida. El aceite resultante se disuelve en acetato de etilo (50 ml). La solución orgánica se lava con agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El aceite resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:1) como eluyente. Se obtiene 2-(4-metansulfonilfenil)-6-metil-3-(2-metilfenoxi)piran-4-ona (0,77 g, 65%) en forma de un sólido blanquecino.

p.f.: 168°C

δ (DMSO): 2.32 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.65 (d, J=7.5 Hz, 1H), 6.89-6.94 (m, 1H), 6.99-7.02 (m, 1H), 7.22 (d, J=7.5 Hz, 1H), 8.06 (d, J=9.0 Hz, 2H), 8.11 (d, J=9.0 Hz, 2H).

EJEMPLO 11

2-(4-Metansulfonilfenil)-6-metil-3-(3-metilfenoxi)piran-4-ona

Se obtiene a partir del compuesto del Ejemplo 5 según el procedimiento descrito en el Ejemplo 10. Por recristalización de etanol/agua (1:2) se obtiene 2-(4-metansulfonilfenil)-6-metil-3-(3-metilfenoxi)piran-4-ona (0,28 g, 29%) en forma de un sólido blnquecino. p.f.: 162°C

δ (DMSO): 2.25 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.73-6.85 (m, 3H), 7.13-7.19 (m, 1H), 8.07 (s, 4H).

EJEMPLO 12

3-(2-Fluoro-4-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-2-ona

Se obtiene a partir del compuesto obtenido en el Ejemplo 6 según el procedimiento descrito en el Ejemplo 10. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (3:2) como eluyente, dando 3-(2-fluoro-4-metilfenoxi)-2-(4-

metansulfonilfenil)-6-metilpiran-2-ona (64%) como un sólido blanco.

p.f.: 171°C

δ (DMSO): 2.24 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 6.47 (s, 1H), 6.83-6.90 (m, 2H), 7.12 (d, J_{F-H}=12.0 Hz, 1H), 8.08 (s, 4H).

EJEMPLO 13

3-(2,4-Difluorofenoxi)-6-etil-2-(4-metansulfonilfenil)-5-metil piran-4-ona

Se obtiene a partir del compuesto obtenido en la Prepararción 18 y anhídrido propiónico según el procedimiento descrito en la Preparación 19. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:2) como eluyente, obteniéndose 3-(2,4-difluorofenoxi)-6-etil-2-(4-metansulfonil fenil)-5-metilpiran-4-ona (21%) en forma de un sólido blanquecino.

p.f.: 200°C

δ (DMSO): 1.29 (t, J=7.5 Hz, 3H), 1.92 (s, 3H), 2.81 (q, J=7.5 Hz, 2H), 3.27 (s, 3H), 6.90-6.96 (m, 1H), 7.02-7.08 (m, 1H), 7.37-7.44 (m, 1H), 8.10 (s, 4H).

EJEMPLO 14

3-Cloro-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona

A una solución del compuesto de la Preparación 19 (0,5 g, 1,28 mmol) en piridina anhidra (10 ml), se añade cloruro de sulfurilo (0,21 ml, 2,56 mmol) gota a gota. La mezcla se agita a temperatura ambiente durante la noche. El crudo de reacción se vierte sobre hielo/ácido clorhídrico 2N (75 ml) y se extrae con acetato de etilo (2 x 100 ml). La fase orgánica se lava con agua (2 x 50 ml) y se seca (Na_2SO_4). El disolvente se elimina a presión reducida y el residuo se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:2) como eluyente. Se obtiene 3-cloro-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona (0,22 g, 40%) en forma de un sólido blanco.

p.f.: 210°C

δ (DMSO): 2.62 (s, 3H), 3.28 (s, 3H), 6.93-6.99 (m, 1H), 7.17-7.22 (m, 1H), 7.39-7.46 (m, 1H), 8.06-8.10 (m, 4H).

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EJEMPLO 15

3-Cloro-5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona

Se obtiene a partir del compuesto de la Preparación 14 según el procedimiento descrito en el Ejemplo 14. Por purificación por cromatografía en columna de gel de sílice y cloruro de metileno/acetato de etilo (9:1) como eluyente, se obtiene 3-cloro-5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona (20%) en forma de un sólido blanquecino.

p.f.: 279°C

δ (DMSO): 2.62 (s, 3H), 3.27 (s, 3H), 7.05-7.17 (m, 4H), 8.08 (s, 4H).

EJEMPLO 16

3-Cloro-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona

Se obtiene a partir del compuesto de la Preparación 20 según el procedimiento descrito en el Ejemplo 14. Por recristalización en etanol se obtiene 3-cloro-5-(4-clorofenoxi)-6-(4-metansulfonil fenil)-2-metilpiran-4-ona (45%) en forma de un sólido blanco.

p.f.: 274°C

δ (DMSO): 2.62 (s, 3H), 3.27 (s, 3H), 7.09 (d, J=6.7 Hz, 2H), 7.36 (d, J=6.7 Hz, 2H), 8.07 (s, 4H).

EJEMPLO 17

5-Bromo-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-6-metil piran-4-ona

A una solución del compuesto obtenido en la Preparación 19 (5,0 g, 12,7 mmol) en cloroformo (100 ml), se añaden piridina (1,10 g, 14,0 mmol) y tribromuro de pridina (10,0 g, 28,0 mmol). La mezcla se agita a temperatura ambiente durante 30 minutos y después se calienta a reflujo durante 92 horas. El crudo se diluye con cloroformo (100 ml), se lava con ácido clorhídrico 2 N (2 x 75 ml) y agua (2 x 75 ml), y se seca (Na_2SO_4). El disolvente se elimina a presión reducida y el residuo se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:1) como eluyente. Se obtiene 5-bromo-3-(2,4-difluorofenoxi)-2-(4-metan

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sulfonilfenil)-6-metilpiran-4-ona (1,10 g, 18%) en forma de un sólido blanco.

p.f.: 230°C

δ (DMSO): 2.67 (s, 3H), 3.28 (s, 3H), 6.92-6.99 (m, 1H), 7.12-7.19 (m, 1H), 7.38-7.46 (m, 1H), 8.07 (s, 4H).

EJEMPLO 18

3-Bromo-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona

Se obtiene a partir del compuesto de la Preparación 20 según el procedimiento descrito en el Ejemplo 17. Por purificación por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:1) como eluyente, se obtiene 3-bromo-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona (10%) en forma de un sólido blanquecino.

p.f.: 251°C

δ (DMSO): 2.67 (s, 3H), 3.27 (s, 3H), 7.08 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 8.07 (s, 4H).

EJEMPLO 19

3-(2,4-Difluorofenoxi)-5,6-dimetil-2-(4-metansulfonilfenil)piran-4-ona

A una solución del compuesto obtenido en el Ejemplo 17 (0,50 g, 1,1 mmol) en dimetilformamida (10 ml) se añaden tetrametilestaño (0,87 ml, 6,3 mmol), tri-o-tolilfosfina (0,20 g, 0,68 mmol), acetato de paladio (0,038 g, 0,17 mmol) y trietilamina (0,30 ml, 2,2 mmol). La mezcla se calienta a 100°C durante 120 horas. Después de enfriar, el crudo se filtra a través Celite® y el disolvente se elimina a presión reducida. El aceite resultante se disuelve en acetato de etilo (50 ml). La solución orgánica se lava con ácido clorhídrico 2 N (2 x 50 ml) y con agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por recristalización en isopropil eter. Se obtiene 3-(2,4-difluorofenoxi)-5,6-dimetil-2-(4-metansulfonilfenil)piran-4-ona (0,25 g, 58%) en forma de un sólido blanquecino.

p.f.: 192°C

δ (DMSO): 1.90 (s, 3H), 2.47 (s, 3H), 3.27 (s, 3H), 6.89-6.94 (m, 1H), 7.00-7.08 (m, 1H), 7.37-7.43 (m, 1H), 8.09 (s, 4H).

EJEMPLO 20

3-(2,4-Difluorofenoxi)-2-(4-metansulfonilfenil)-6-metil-5-vinil piran-4-ona

A una solución del compuesto obtenido en el Ejemplo 17 (0,50 g, 1,1 mmol) en dimetilformamida (10 ml) se añaden tributil vinil estaño (1,24 ml, 4,24 mmol), tri-o-tolilfosfina (0,10 g, 0,34 mmol), acetato de paladio (0,019 g, 0,084 mmol) y trietilamina (0,15 ml, 1,1 mmol). La mezcla se calienta a 100°C toda una noche. Después de enfriar, el crudo se filtra a través de Celite® y se diluye con acetato de etilo (50 ml). La solución orgánica se lava con ácido clorhídrico 2 N (2 x 50 ml) y agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:3) como eluyente. Se obtiene 3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metil-5-vinil piran-4-ona (0,25 g, 57%) en forma de un sólido blanco.

p.f.: 184°C

δ ($CDCl_3$): 2.60 (s, 3H), 3.10 (s, 3H), 5.59 (dd, J=2.0 Hz, J=11.6 Hz, 1H), 6.18 (dd, J=2.0 Hz, J=17.4 Hz, 1H), 6.48 (dd, J=11.6 Hz, J=17.4 Hz, 1H), 6.68-6.95 (m, 3H), 8.04 (d, J=8.7 Hz, 2H), 8.15 (d, J=8.7 Hz, 1H).

EJEMPLO 21

3-(2,4-Difluorofenoxi)-5-etil-2-(4-metansulfonilfenil)-6-metil piran-4-ona

A una solución del compuesto del Ejemplo 20 (0,14 g, 0,33 mmol) en acetato de etilo (25 ml) y metanol (50 ml) se añade paladio sobre carbón activo (14 mg, 10%). La mezcla se hidrogena a temperatura ambiente y a 30 psi durante 1 hora. El crudo se filtra a través de Celite® y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:3) como eluyente. Se obtiene 3-(2,4-difluorofenoxi)-5-etil-2-(4-metansulfonilfenil)-6-metil piran-4-ona (0,063 g, 45%) en forma de un sólido blanquecino.

p.f.: 173°C

δ (CDCl3): 1.09 (t, J=7.5 Hz, 3H), 2.47 (s, 3H), 2.49 (q, J=7.5 Hz, 2H), 3.09 (s, 3H), 6.72-6.75 (m, 1H), 6.81-6.91 (m, 2H), 8.03 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.5 Hz, 2H).

EJEMPLO 22

3-(2,4-Difluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona

A una solución del compuesto obtenido en la Preparación 21 (1,36 g, 3,3 mmol) en metanol (20 ml), se añade lentamente hidruro de boro y sodio (0,19 g, 5,2 mmol) a 0°C. La mezcla resultante se agita durante 30 minutos a temperatura ambiente. La mezcla de reacción se concentra y el residuo se disuelve en acetato de etilo. La fase orgánica se lava con agua, se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:1) como eluyente. Se obtiene 3-(2,4-difluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona (0,65 g, 48%) en forma de un sólido blanco.

p.f.: 205°C

δ (DMSO): 3.27 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.90 (t, J=6.0 Hz, 1H), 6.52 (s, 1H), 6.61-6.67 (m, 1H), 7.07-7.14 (m, 1H), 7.37-7.43 (m, 1H), 8.09 (s, 4H).

EJEMPLO 23

3-(4-Fluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona

Se obtiene a partir del compuesto obtenido en la Preparación 22 según el procedimiento descrito en el Ejemplo 22. Se recristaliza en etanol obteniéndose 3-(4-fluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona (30%) en forma de un sólido blanquecino.

p.f.: 206°C

δ (DMSO): 3.27 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.91 (t, J=6.0 Hz, 1H), 6.52 (s, 1H), 6.98-7.04 (m, 2H), 7.10-7.16 (m, 2H), 8.06 (d, J=8.0 Hz, 2H), 8.10 (d, J=8.0 Hz, 2H).

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EJEMPLO 24

3-(4-Clorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona

Se obtiene a partir del compuesto obtenido en la Preparación 23 según el procedimiento descrito en el Ejemplo 22. Se recristaliza en etanol obteniéndose 3-(4-clorofenoxi)-6-hidroximetil-2-(4-metan sulfonilfenil)piran-4-ona (49%) en forma de un sólido blanquecino.
p.f.: 227°C

δ (DMSO): 3.26 (s, 3H), 4.50 (d, J=6.0 Hz, 2H), 5.91 (t, J=6.0 Hz, 1H), 6.53 (s, 1H), 7.04 (d, J=7.0 Hz, 2H), 7.34 (d, J=7.0 Hz, 2H), 8.07 (s, 4H).

EJEMPLO 25

3-(2-Fluoro-4-bromofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona

Se obtiene a partir del compuesto de la Preparación 24 según el procedimiento descrito en el Ejemplo 22. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo, obteniéndose 3-(2-fluoro-4-bromofenoxi)-6-hidroximetil-2-(4-metan sulfonilfenil)piran-4-ona (34%) en forma de un sólido blanquecino.
p.f.: 202-203°C

δ ($CDCl_3$):3.08 (s, 3H), 4.64 (s, 2H), 6.62 (s, 1H), 6.74 (t, J=8.9 Hz, 1H), 7.12 (dd, J=1.5 Hz, J=8.9 Hz, 1H), 7.29 (dd, J=2.4 Hz, J=10.5 Hz, 1H), 8.02 (d, J=8.9 Hz, 2H), 8.08 (d, J=8.9 Hz, 2H).

EJEMPLO 26

3-(2,4-Difluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetil piran-4-ona

A una solución del compuesto obtenido en el Ejemplo 22 (0,64 g, 1,6 mmol) en cloruro de metileno (30 ml) y tetrahidrofurano (20 ml) se añaden ioduro de metilo (0,29 ml, 4,7 mmol) y una solución de hidróxido sódico (0,50 g, 12,5 mmol) y cloruro de tetrabutilamonio (50 mg) en agua (1 ml). La mezcla de reacción se agita a temperatura ambiente dutante 18 horas. La fase orgánica se diluye con cloruro de metileno (30 ml), se lava con agua, se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El sólido resultante se purifica por cromatografía en columna de gel de

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sílice y cloruro de metileno/acetato de etilo/ácido acético (78:10:1) como eluyente. Se obtiene 3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona (0,09 g, 14%) en forma de un sólido blanquecino.

p.f.: 124°C

δ (DMSO): 3.27 (s, 3H), 3.43 (s, 3H), 4.47 (s, 2H), 6.57 (s, 1H), 6.70-6.94 (m, 1H), 7.10-7.18 (m, 1H), 7.39-7.43 (m, 1H), 8.06 (d, J=9.0 Hz, 2H), 8.11 (d, J=9.0 Hz, 2H).

EJEMPLO 27

3-(4-Fluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona

A una solución del compuesto del Ejemplo 23 (0,74 g, 0,9 mmol) en metanol (50 ml) se añaden yoduro de metilo (0,36 ml, 5,8 mmol) y óxido de plata recientemente preparado (1,75 g, 7,59 mmol). La mezcla de reacción se agita a temperatura ambiente durante 18 horas. El crudo se filtra a través de Celite® y se lava con metanol (3 x 25 ml). La solución orgánica se lava con hidróxido amónico diluído (2 x 50 ml) y agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y cloruro de metileno/acetato de etilo/ácido acético (78:10:1) como eluyente. Se obtiene 3-(4-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona (0,40 g, 52%) en forma de un sólido blanco.

p.f.: 165°C

δ (DMSO): 3.27 (s, 3H), 3.43 (s, 3H), 4.48 (s, 2H), 6.57 (s, 1H), 7.05-7.13 (m, 4H), 8.07 (s, 4H).

EJEMPLO 28

3-(4-Clorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona

Se obtiene a partir del compuesto obtenido en el Ejemplo 24 según el procedimiento descrito en el Ejemplo 27. Se purifica por cromatografía en columna de gel de sílice y cloruro de metileno/metanol (99:1) como eluyente dando 3-(4-clorofenoxi)-2-

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(4-metansulfonilfenil)-6-metoximetilpiran-4-ona (4%) en forma de un sólido blanco.

p.f.: 136°C

δ (DMSO): 3.26 (s, 3H), 3.42 (s, 3H), 4.47 (s, 2H), 6.58 (s, 1H), 7.05 (d, J=7.5 Hz, 2H), 7.35 (d, J=7.5 Hz, 2H), 8.04 (d, J=9.0 Hz, 2H), 8.08 (d, J=9.0 Hz, 2H).

EJEMPLO 29

Acetato de [5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo

A una disolución del compuesto del Ejemplo 22 (0,75 g, 1,8 mmol) en cloruro de metileno (10 ml) se añaden trietilamina (0,28 ml, 2,0 mmol) y cloruro de acetilo (0,14 ml, 2,02 mmol). La mezcla se agita a temperatura ambiente durante 4 horas. El crudo se vierte sobre hielo y se diluye con cloruro de metileno (50 ml). La solución orgánica se lava con bicarbonato sódico (4%, 2 x 50 ml) y agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:1) como eluyente. Se obtiene el acetato de [5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il] metilo (0,39 g, 47%) en forma de un sólido blanco.

p.f.: 175°C

δ (DMSO): 2.17 (s, 3H), 3.28 (s, 3H), 5.14 (s, 2H), 6.68 (s, 1H), 6.94-6.97 (m, 1H), 7.09-7.16 (m, 1H), 7.36-7.44 (m, 1H), 8.06-8.12 (m, 4H)

EJEMPLO 30

Acetato de [5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo

Se obtiene a partir del compuesto del Ejemplo 23 según el procedimiento descrito en el Ejemplo 29. Por purificación por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (3:2) como eluyente, se obtiene el acetato de [5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo (47%) en forma de sólido blanquecino.

p.f.: 180°C

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δ (DMSO): 2.17 (s, 3H), 3.27 (s, 3H), 5.14 (s, 2H), 6.69 (s, 1H), 7.01-7.06 (m, 2H), 7.10-7.16 (m, 2H), 8.08 (s, 4H).

EJEMPLO 31

Acetato de [5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo

Se obtiene a partir del compuesto del Ejemplo 24 según el procedimiento descrito en el Ejemplo 29. Por purificación por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:1) como eluyente, se obtiene el acetato de [5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo (47%) en forma de un sólido blanquecino.

p.f.: 115°C

δ (DMSO): 2.17 (s, 3H), 3.27 (s, 3H), 5.15 (s, 2H), 6.69 (s, 1H), 7.05 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H), 8.07 (s, 4H).

EJEMPLO 32

Acido 5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico

A una solución enfriada del compuesto de la Preparación 21 (1,50 g, 3,69 mmol) en acetona (6 ml) se añade una solución de óxido de cromo(VI) (0,41 g, 4,1 mmol) y ácido sulfúrico (3.5 ml) en agua (3 ml). La mezcla se agita a 0°C durante 1 hora y a temperatura ambiente durante 16 horas. El disolvente se elimina a presión reducida y el residuo se disuelve en acetato de etilo (50 ml). La solución orgánica se lava con agua e hidróxido sódico 2 N (2 x 50 ml). La fase alcalina se acidifica con ácido clorhídrico 2 N y se extrae con acetato de etilo (2 x 50 ml). Los extractos orgánicos combinados se lavan con agua (2 x 50 ml), se secan (Na_2SO_4), y el disolvente se elimina a presión reducida. El sólido resultante se recristaliza en etanol dando el ácido 5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico (0,20 g, 13%) en forma de un sólido blanco.

p.f.: 245°C

δ (DMSO): 3.28 (s, 3H), 6.93-6.98 (m, 1H), 7.12 (s, 1H), 7.14-7.24 (m, 1H), 7.39-7.46 (m, 1H), 8.09 (d, J=8.5 Hz, 2H), 8.14 (d, J=8.5 Hz, 2H).

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EJEMPLO 33

Acido 5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico

Se obtiene a partir del compuesto de la Preparación 23 según el procedimiento descrito en el Ejemplo 32. Se recristaliza en acetato de etilo, obteniéndose el ácido 5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico (25%) en forma de un sólido blanquecino.

p.f.: 263°C

δ (DMSO): 3.27 (s, 3H), 7.11 (d, J=9.0 Hz, 2H), 7.12 (s, 1H), 7.35 (d, J=9.0 Hz, 2H), 8.05-8.10 (m, 4H).

EJEMPLO 34

6-(1,1-Difluorometil)-3-(2,4-difluorofenoxi)-2-(4-metansulfonil fenil)piran-4-ona

A una disolución enfriada del compuesto de la Preparación 21 (1,0 g, 2,5 mmol) en cloruro de metileno (15 ml) se añade trifluoruro de dietilaminoazufre (0,39 ml, 2,9 mmol). La mezcla se agita a 0°C durante 1 hora y a temperatura ambiente durante 16 horas. La mezcla se diluye con cloruro de metileno (50 ml). La solución orgánica se lava con agua (2 x 50 ml), se seca (Na_2SO_4), y el disolvente se elimina a presión reducida. El residuo resultante se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:3) como eluyente. Se obtiene 6-(1,1-difluorometil)-3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil) piran-4-ona (0,20 g, 18%) en forma de un sólido blanquecino.

p.f.: 156°C

δ (DMSO): 3.28 (s, 3H), 6.93-6.99 (m, 1H), 7.00 (s, 1H), 7.12 (t, J_{F-H}=54 Hz, 1H), 7.22-7.30 (m, 1H), 7.38-7.46 (m, 1H), 8.07 (d, J=9.0 Hz, 2H), 8.12 (d, J=9.0 Hz, 2H).

EJEMPLO 35

6-(1,1-Difluorometil)-3-(4-bromofenoxi)-2-(4-metansulfonilfenil) piran-4-ona

Se obtiene a partir del compuesto de la Preparación 24 según el procedimiento descrito en el Ejemplo 34. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-

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hexano (1:1) como eluyente, obteniéndose 6-(1,1-difluorometil)-3-(4-bromofenoxi)-2-(4-metansulfonilfenil)piran-4-ona (0,58, 48%) en forma de un sólido blanquecino.

LRMS: m/z 471 $(M+1)^+$.

δ ($CDCl_3$): 3.08 (s, 3H), 6.53 (t, J_{F-H}=78 Hz, 1H), 6.85 (d, J=9.0 Hz, 2H), 7.40 (d, J=9.0 Hz, 2H), 8.00-8.11 (m, 4H).

EJEMPLO 36

6-(1,1-Difluorometil)-2-(4-metansulfonilfenil)-3-(4-metilfenoxi) piran-4-ona

Se obtiene a partir del compuesto del Ejemplo 35 según el procedimiento descrito en el Ejemplo 10. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (2:3) como eluyente, obteniéndose 6-(1,1-difluorometil)-2-(4-metansulfonilfenil)-3-(4-metilfenoxi)piran-4-ona (0,20 g, 18) en forma de un sólido blanquecino.

p.f.: 160°C

δ (DMSO): 2.23 (s, 3H), 3.26 (s, 3H), 6.93 (d, J=9.0 Hz, 2H), 6.98 (s, 1H), 7.09 (d, J=9.0 Hz, 2H), 7.11 (t, J_{F-H}=54 Hz, 1H), 8.04-8.11 (m, 4H).

EJEMPLO 37

3-Bromo-2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metan sulfonilfenil)piran-4-ona

Se obtiene a partir del compuesto del Ejemplo 34 según el procedimiento descrito en el Ejemplo 17. Se purifica por cromatografía en columna de gel de sílice y acetato de etilo/n-hexano (1:2) como eluyente, obteniéndose 3-bromo-2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil) piran-4-ona (13%) en forma de un sólido blanquecino.

LRMS: m/z 507 $(M+1)^+$.

δ (DMSO): 3.13 (s, 3H), 6.71-7.13 (m, 4H), 8.11 (d, J=9.0 Hz, 2H), 8.25 (d, J=9.0 Hz, 2H).

EJEMPLO 38

2-(1,1-Difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metansulfonil fenil)-3-metilpiran-4-ona

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Se obtiene a partir del compuesto del Ejemplo 37 según el procedimiento descrito en el Ejemplo 19. Por recristalización en etanol se obtiene 2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-3-metilpiran-4-ona (86%)en forma de un sólido blanquecino.

p.f.: 187.8-188.6°C

δ ($CDCl_3$): 2.14 (s, 3H), 3.09 (s,3H), 6.56-6.93 (m, 4H), 8.07 (d, J=8.7 Hz, 2H), 8.19 (d, J=8.7 Hz, 2H).

Los ejemplos 39 y 40 ilustran las composiciones farmacéuticas de acuerdo con la presente invención y procedimientos para su preparación.

EJEMPLO 39

Cápsulas

25.000 Cápsulas cada una conteniendo 100 mg de 3-(4-fluoro-2-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona (ingrediente activo), se preparan de acuerdo con la siguiente formulación:

Ingrediente activo	2,5	kg
Lactosa monohidrato	5	kg
Dióxido de silicio coloidal	0,05	kg
Almidón de maíz	0,5	kg
Estearato magnésico	0,1	kg

Procedimiento

Los anteriores ingredientes se tamizan a través de un tamiz de 60 mallas, y se mezclan en un mezclador apropiado y se llenan en 25.000 cápsulas de gelatina.

EJEMPLO 40

Comprimidos

100.000 Comprimidos conteniendo cada uno 50 mg de 3-(2,4-difluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona (ingrediente activo), se preparan a partir de la siguiente formulación:

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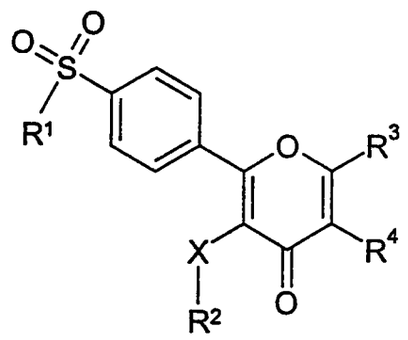
REIVINDICACIONES

1. Un compuesto de fórmula (I):

(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquilmetoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un átomo de hidrógeno, o un grupo alquilo, alquenilo o alquinilo o un átomo de halógeno; y

X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

2. Un compuesto de fórmula (I):

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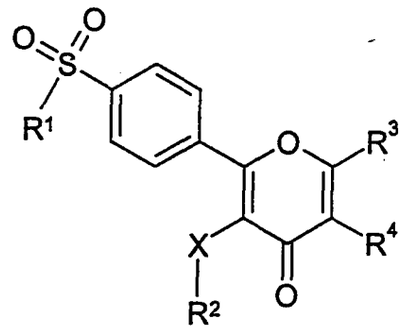
(I) 

en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 and R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquilmetoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un átomo de hidrógeno, o un grupo alquilo, alquenilo o alquinilo o un átomo de halógeno; y

X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno; con la condición de que cuando R^4 es un átomo de hidrógeno, R^3 es un grupo alquenilmetoximetil, C_3-C_7 cicloalquilmetoximetilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo; o una sal farmacéuticamente aceptable de los mismos.

3. Un compuesto de fórmula (I):

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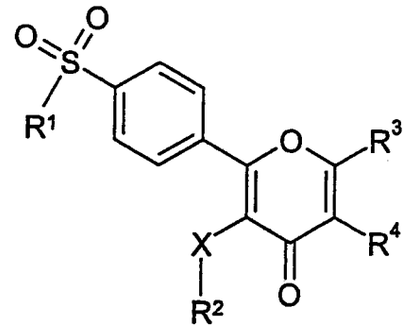
(I)



en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, alqueniloximetilo, C_3-C_7 cicloalcoximetilo, C_3-C_7 cicloalquilmetoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un grupo alquilo, alquenilo o alquinilo o un átomo de halógeno; y

X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

4. En otro aspecto preferido, la presente invención se refiere a un compuesto de fórmula (I):

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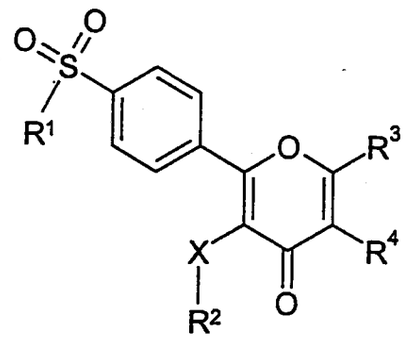

(I)

en donde:

R^1 representa un grupo alquilo o un grupo $-NR^5R^6$, en donde R^5 y R^6 cada uno independientemente representan un átomo de hidrógeno o un grupo alquilo;

R^2 representa un grupo alquilo, C_3-C_7 cicloalquilo, piridilo, tienilo, naftilo, tetrahidronaftilo o indanilo, o un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más átomos de halógeno o un grupo alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alqueniloximetilo o C_3-C_7 cicloalquilmetoximetilo o un grupo R^7-COO-CH_2- en donde R^7 representa un grupo alquilo o un grupo fenilo;

R^4 representa un átomo de hidrógeno; y

X representa un enlace sencillo, un átomo de oxígeno, un átomo de azufre o un grupo metileno;

o una sal farmacéuticamente aceptable de los mismos.

5. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 4 en donde R^1 representa un grupo alquilo no sustituido o un NH_2.

6. Un compuesto de acuerdo con la reivindicación 5 en donde R^1 es un grupo metilo.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 6 en donde X representa un átomo de oxígeno.

8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 2, 3, 5, 6 o 7 en donde R^3 representa un grupo C_{1-3} alquilo no sustituido, hidroximetilo, metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, difluorometilo, propeniloximetilo, hidroxicarbonilo, ciclopropoximetilo, ciclobutoximetilo, ciclopropilmetoximetilo, ciclobutilmetoximetilo o CH_3-COO-CH_2-.

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 8 en donde R^3 es un grupo propeniloximetilo, ciclopropilmetoximetilo, ciclobutilmetoximetilo o CH_3-COO-CH_2-.

10. Un compuesto de acuerdo con cualquiera de las reivindicaciones 2, 3, 5, 6, 7, 8 o 9 en donde R^4 es un átomo de cloro o bromo o un grupo metilo, etilo, etenilo o etinilo.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 10 en donde R^2 es un grupo alquilo ramificado, C_3-C_7 cicloalquilo, naftilo, tetrahidronaftilo o indanilo, un grupo fenilo no sustituido o un grupo fenilo sustituido por uno o más átomos de halógeno, grupos alquilo y/o grupos alcoxi.

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 11 en donde R^2 es un grupo fenilo no sustituido o un grupo fenilo sustituido por 1, 2 o 3 sustituyentes independientemente seleccionados de átomos de halógeno, grupos metoxi o grupos metilo.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 12 en donde R^2 representa un grupo fenilo sustituido por 1 o 2 sustituyentes independientemente seleccionados de átomos de halógeno y grupos metilo.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 13 en donde R^2 es un grupo 2,4-difluorofenilo.

15. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 2 a la 14 que es:

3-(2,4-difluorofenoxi)-6-etil-2-(4-metansulfonilfenil)-5-metil piran-4-ona;

3-cloro-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona;

3-cloro-5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-cloro-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-bromo-5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-2-metil piran-4-ona;

3-bromo-5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-2-metilpiran-4-ona;

3-(2,4-difluorofenoxi)-5,6-dimetil-2-(4-metansulfonilfenil)piran-4-ona;

3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metil-5-vinil piran-4-ona;

3-(2,4-difluorofenoxi)-5-etil-2-(4-metansulfonilfenil)-6-metil piran-4-ona;

3-bromo-2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metan sulfonilfenil)piran-4-ona;

2-(1,1-difluorometil)-5-(2,4-difluorofenoxi)-6-(4-metan-sulfonil fenil)-3-metilpiran-4-ona;

acetato de [5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

acetato de [5-(4-fluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

acetato de [5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-il]metilo;

o sales farmacéuticamente aceptables de los mismo.

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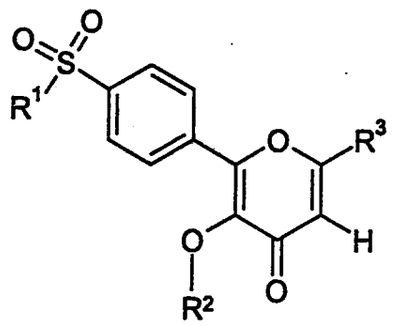
16. Un compuesto de fórmula (IA):

(IA)



en donde:

R^1 representa un grupo metilo o etilo;

R^2 representa un grupo fenilo el cual puede estar no sustituido o sustituido por uno o más sustituyentes seleccionados entre átomos de halógeno o grupos alquilo, trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo;

R^3 representa un grupo alquilo, hidroximetilo, alcoximetilo, C_3-C_7 cicloalcoximetilo, benciloximetilo, hidroxicarbonilo, nitrilo, trifluorometilo o difluorometilo;

a condición de que cuando R^3 es metilo, R^2 es (a) un grupo fenilo que tiene al menos un sustituyente seleccionado entre los grupos trifluorometilo, hidroxi, alcoxi, metiltio, amino, mono- o dialquilamino, hidroxialquilo o hidroxicarbonilo, (b) un grupo fenilo monosustituido que tiene un átomo de halógeno o un grupo alquilo en la posición 3 o que tiene un átomo de bromo o un grupo alquilo en la posición 2 o (c) un grupo fenilo que tiene dos o más sustituyentes en donde al menos un sustituyente es un átomo de bromo o en donde un grupo alquilo está presente en la posición 2 o 4, (d) 3-metil-4-fluorofenilo,

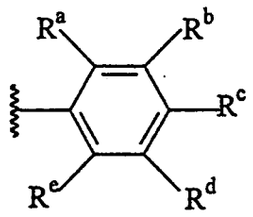
o una sal farmacéuticamente aceptable de los mismos.

17. Un compuesto de acuerdo con la reivindicación 16 en donde R^3 es un grupo etilo, propilo, hidroximetilo, metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, difluorometilo, hidroxicarbonilo, ciclopropoximetilo o ciclobutoximetilo.

18. Un compuesto de acuerdo con la reivindicación 16 o 17 en donde R^3 es un grupo hidroximetilo, metoximetilo o hidroxicarbonilo.

19. Un compuesto de acuerdo con las reivindicaciones 17 o 18 en donde R^2 es un grupo fenilo no sustituido o un grupo fenilo sustituido por un átomo de halógeno seleccionado de flúor, cloro o bromo, un grupo metilo o dos átomos de halógeno los cuales son iguales o diferentes y seleccionados de flúor, cloro o bromo.

20. Un compuesto de acuerdo con la reivindicación 19 en donde R^2 representa un grupo de fórmula



en donde R^a, R^b, R^c, R^d y R^e son como se definen a continuación

R^a	R^b	R^c	R^d	R^e
H	H	H	H	H
H	H	F	H	H
H	F	H	H	H
F	H	H	H	H
H	H	Cl	H	H
H	Cl	H	H	H
Cl	H	H	H	H
H	H	Br	H	H
H	Br	H	H	H
Br	H	H	H	H
H	H	Me	H	H
H	Me	H	H	H
Me	H	H	H	H
F	H	F	H	H
F	H	H	F	H
H	F	F	H	H
F	H	H	H	F

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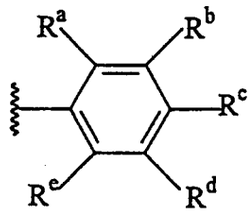
Cl	H	Cl	H	H
Cl	H	H	Cl	H
H	Cl	Cl	H	H
Cl	H	H	H	Cl
F	H	Cl	H	H
Cl	H	F	H	H
F	H	Br	H	H
Cl	H	Br	H	H
Br	H	Br	H	H
Br	H	F	H	H
H	Cl	F	H	H
H	F	Cl	H	H
F	H	Me	H	H
Cl	H	Me	H	H
Me	H	F	H	H
Me	H	Cl	H	H
H	Me	F	H	H
H	Me	Cl	H	H
H	F	Me	H	H
H	Cl	Me	H	H

21. Un compuesto de acuerdo con la reivindicación 16 en donde R^3 es un grupo metilo y R^2 es un grupo de fórmula



en donde R^a, R^b, R^c, R^d y R^e se definen como:

R^a	R^b	R^c	R^d	R^e
H	Br	H	H	H
Br	H	H	H	H
H	Me	H	H	H
Me	H	H	H	H
Me	H	F	H	H
Me	H	Cl	H	H
F	H	Me	H	H
Cl	H	Me	H	H
H	Me	F	H	H
H	F	Me	H	H
H	Cl	Me	H	H
F	H	Br	H	H
Cl	H	Br	H	H
Br	H	Br	H	H

22. Un compuesto de acuerdo con la reivindicación 16 que es
3-(4-fluoro-2-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(4-cloro-2-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(2-cloro-4-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(2-bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(3-bromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(4-bromo-2-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;

3-(4-bromo-2-clorofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(2,4-dibromofenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(2,4-difluorofenoxi)-2-(4-etansulfonilfenil)-6-metilpiran-4-ona;
2-(4-metansulfonilfenil)-6-metil-3-(2-metilfenoxi)piran-4-ona;
2-(4-metansulfonilfenil)-6-metil-3-(3-metilfenoxi)piran-4-ona;
3-(2-fluoro-4-metilfenoxi)-2-(4-metansulfonilfenil)-6-metilpiran-4-ona;
3-(2,4-difluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona;
3-(4-fluorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona;
3-(4-clorofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil)piran-4-ona;
3-(2-fluoro-4-bromofenoxi)-6-hidroximetil-2-(4-metansulfonilfenil) piran-4-ona;
3-(2,4-difluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran -4-ona;
3-(4-fluorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona;
3-(4-clorofenoxi)-2-(4-metansulfonilfenil)-6-metoximetilpiran-4-ona;
ácido 5-(2,4-difluorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico;
ácido 5-(4-clorofenoxi)-6-(4-metansulfonilfenil)-4-oxo-4H-piran-2-carboxílico;
6-(1,1-difluorometil)-3-(2,4-difluorofenoxi)-2-(4-metansulfonil fenil)piran-4-ona;
6-(1,1-difluorometil)-3-(4-bromofenoxi)-2-(4-metansulfonilfenil) piran-4-ona;
6-(1,1-difluorometil)-2-(4-metansulfonilfenil)-3-(4-metilfenoxi) piran-4-ona;
o una sal farmacéuticamente aceptable de los mismos.

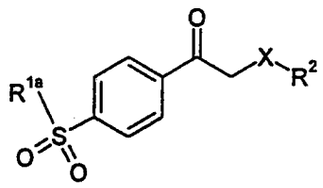
23. Un procedimiento para obtener un compuesto de fórmula (I) tal como se define en cualquiera de las reivindicaciones de la 1 a la 15 o un compuesto de fórmula (IA) tal como se define en cualquiera

de las reivindicaciones de la 16 a la 22, que comprende un procedimiento:

(a) en donde R^1 es un grupo alquilo o un grupo $-NR^5R^6$ en que R^5 y R^6 son cada uno independientemente grupos alquilo, y R^3 es un grupo metilo, R^4 es un átomo de hidrógeno y R^2 y X son tal como se define anteriormente, que comprende

ai) la reacción de un derivado carbonílico (III):

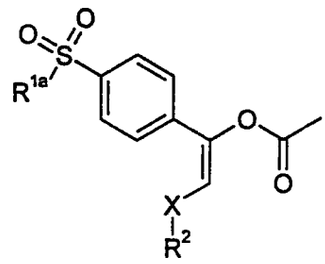
(III)



en donde R^{1a} es un grupo alquilo o un grupo $-NR^{5a}R^{6a}$ en que R^{5a} y R^{6a} son cada uno independientemente grupos alquilo y R^2 y X son como se ha definido en las reivindicaciones anteriores, con un exceso de ácido acético anhidro o anhídrido acético y ácido polifosfórico, a una temperatura desde 90°C hasta 150°C; o

aii) la reacción de un derivado vinílico de fórmula (IV):

(IV)



en donde R^{1a}, R^2 y X somo como se ha definido anteriormente, con un exceso de anhídrido acético y ácido polifosfórico a una temperatura desde 80°C hasta 120°C;

(b) en donde R^1 es un grupo alquilo o un grupo $-NR^5R^6$ en que R^5 y R^6 son grupos alquilo, R^4 es un grupo alquilo, R^3 es un grupo alquilo de fórmula CH_2-R^4 y R^2 y X son como se ha definido en las reivindicaciones anteriores,

bi) haciendo reaccionar un derivado carbonílico de fórmula (III) con un exceso de un anhídrido de fórmula (IX):

(IX) $(R^{4a}CH_2CO)_2O$

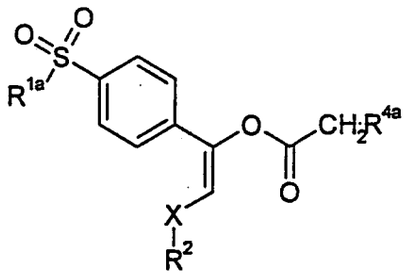
o un ácido carboxílico de fórmula (X):

(X) $R^{4a}CH_2COOH$

y ácido polifosfórico a una temperatua desde 90°C hasta 150°C; o

bii) haciendo reaccionar un derivado vinílico de fórmula (XI):

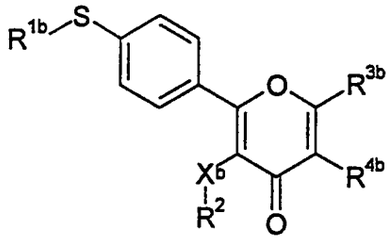
(XI)



en donde R^{1a}, R^2, R^4 y X son como se ha definido anteriormente, con un exceso de un anhídrido de fórmula (IX) y ácido polifosfórico a una temperatura desde 90°C hasta 150°C;

(c) en donde R^1 es un grupo alquilo, R^3 es un grupo alquilo, R^4 es un átomo de hidrógeno o un grupo alquilo, y X es tal como se define en cualquiera de las reivindicaciones de la 1 a la 22 con la condición de que es diferente a un átomo de azufre y R^2 es como se ha definido en cualquiera de las reivindicaciones de la 1 a la 22, por reacción de un mercapto derivado de fórmula (XIII):

(XIII)



en donde R^{1b} es un grupo alquilo, R^{3b} es un grupo metilo o un grupo $R^{4b}CH_2$, R^{4b} es un átomo de hidrógeno o un grupo alquilo, X^b es tal como se define para X en cualquiera de las reivindicaciones de la 1 a la 22 con la condición de que es diferente a un átomo de azufre y R^2 es tal como se ha definido anteriormente, con un agente oxidante;

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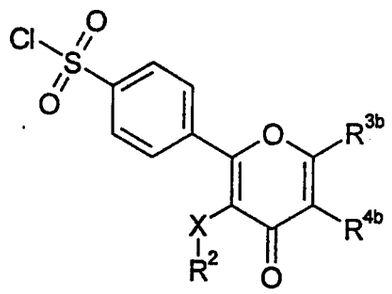
(d) en donde R^1 es un grupo $-NR^5R^6$, R^3 es un grupo alquilo, R^4 es un átomo de hidrógeno o un grupo alquilo, R^2, R^5, R^6 y X son como se ha definido en las reivindicaciones de la 1 a la 22, por reacción de un derivado clorosulfonilo de fórmula (XV):

(XV)



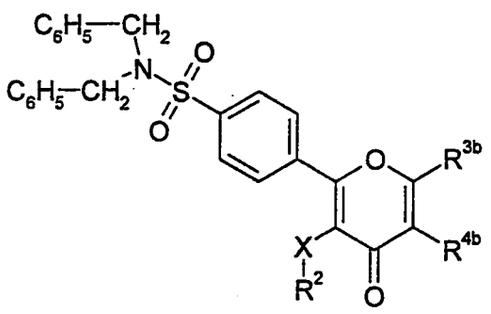
en donde R^2, R^{3b}, R^{4b} y X son como se ha definido anteriormente, con una amina de fórmula (XVI):

(XVI) R^5-NH-R^6

en donde R^5 y R^6 son como se ha definido anteriormente;

(e) en donde R^1 es un grupo $-NR^5R^6$ en donde R^5 y R^6 son hidrógeno, R^3 es un grupo alquilo y R^4 es un átomo de hidrógeno o un grupo alquilo, por desbencilación del correspondiente derivado N,N-dibencílico de fórmula (XIX):

(XIX)



en donde R^2, R^{3b}, R^{4b} y X son como se define anteriormente;

(f) en donde R^4 es diferente de un átomo de hidrógeno, por reacción de un compuesto de fórmula (XXXIII):

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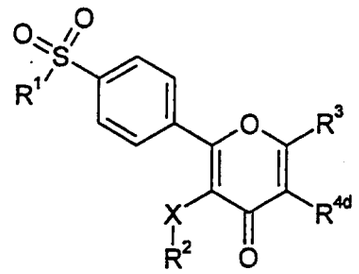
(XXXIII) 

en donde R^{4d} es un átomo de cloro, bromo o yodo, preferentemente un átomo de bromo y R^1, R^2, R^3 y X son como se ha definido en las reivindicaciones anteriores, con un derivado de estaño de fórmula (XXXIV):

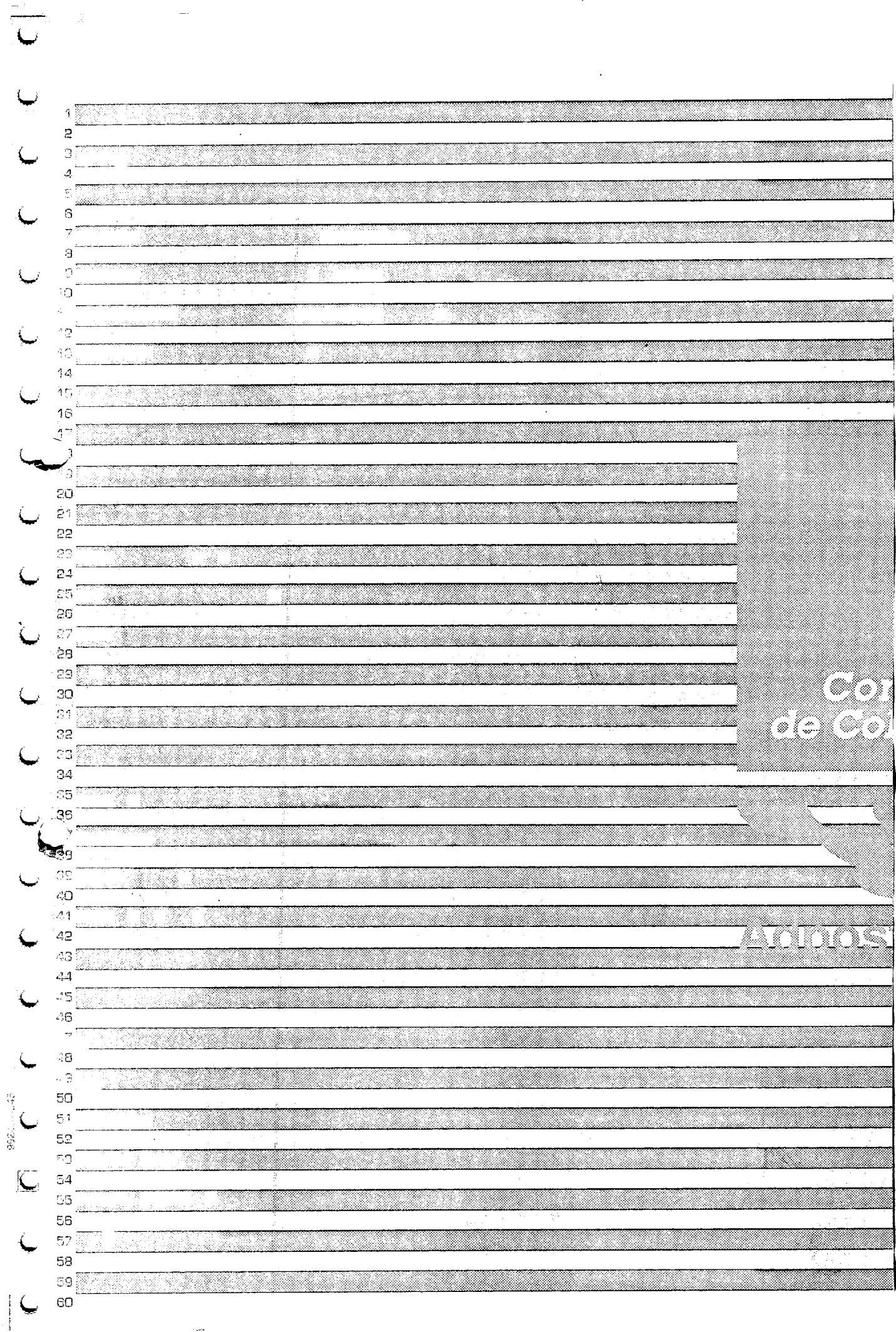
(XXXIV) $$R^{4c}\ Sn\ (R^9)_3$$

en donde R^{4c} es un grupo alquilo, alquenilo o alquinilo y R^9 es un grupo alquilo.

24. Una composición farmacéutica que comprende un compuesto de acuerdo con cualquiera de las reivindicaciones de la 1 a la 22 o una sal farmacéuticamente aceptable del mismo mezclado con un excipiente o diluyente farmacéuticamente aceptable.

25. Un compuesto de acuerdo con cualquiera de las reivindicaciones de la 1 a la 22 o una composición de acuerdo con la reivindicación 24, para uso en un método de tratamiento terapéutico para el cuerpo humano o animal.

26. El uso de un compuesto de acuerdo con cualquiera de las reivindicaciones de la 1 a la 22 o una composición de acuerdo con la reivindicación 24, para la fabricación de un medicamento para uso en el tratamiento del dolor, fiebre o inflamación mediante la inhibición de prostanoides que inducen la contracción del músculo liso o para la prevención o tratamiento del cancer colorectal o enfermedades neurodegenerativas.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RECIBO OFICIAL DE CAJA : 02 - 56,220
FECHA : AGOSTO 26 DE 2002

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	3344171	26/08/2002	34,463,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	7 TRAMITES DE SOL. DE DISENOS INDUS	378,000.00
		TOTAL : $	378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPO : _____

RECI E CAJA APLICADO AL EXPEDIENTE No._____

C.b 13440-B41-001-4

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REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

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PATENTE DE INVENCIÓN [ ] **MODELO DE UTILIDAD**	[ ]	[ ]
• Indicación de que se solicita la concesión de una patente	[ ]	[ ]
• Datos de identificación del solicitante o de la persona que presenta la solicitud	[ ]	[ ]
• Descripción de la invención	[ ]	[ ]
• Dibujos de ser estos pertinentes	[ ]	[ ]
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• Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño.	[ ]	[ ]
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• Representación gráfica del esquema de trazado	[ ]	[ ]
• Comprobante de pago de las tasas establecidas.	[ ]	[ ]
COMPLETA [ ] INCOMPLETA	[ ]	[ ]

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