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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.

WO 03/047561 A1

(54) Title: USE OF 4-OXOBUTANOIC ACID DERIVATIVES IN THE TREATMENT OF INFLAMMATION

(57) Abstract: The present invention relates to the use of a 4-oxobutanoic acid derivative for the preparation of a pharmaceutical composition for treating inflammation.

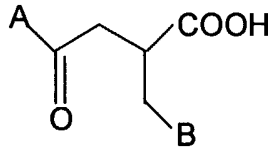
Use of 4-oxobutanoic acid derivatives in the treatment of inflammation

The present invention relates to the use of a 4-oxobutanoic acid derivative for the preparation of a pharmaceutical composition for treating inflammation.

4-Oxobutanoic acid derivatives have already been described in patent application WO 98/07681 as antidiabetic agents and more particularly for treating non-insulin-dependent diabetes.

Thus, the present patent application relates firstly to the use of at least one 4-oxobutanoic acid derivative conforming to the general formula (I) for the preparation of a medicament for treating inflammation.

The compound of the formula (I) is defined as follows:



(I)

in which the groups A and B are chosen, independently of each other, from:

- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl groups;
- an alkyl group containing from 1 to 14 carbon atoms;
- a cycloalkyl group containing from 5 to 8 carbon atoms;
- a saturated heterocyclic group chosen from tetrahydrofuryl, tetrahydropyranyl, piperidyl and pyrrolidinyl groups;

where the groups A and B may carry from 1 to 3 substituents chosen from a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_6-C_{14} aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl, a (C_6-C_{14})aryl(C_1-C_6)alkyl group, a (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)-

alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylsulfonyl, sulfoamino, (C_1-C_6)alkylsulfonyl-amino, sulfamoyl or (C_1-C_6)alkylcarbonylamino group;

or two of the substituents form a methylenedioxy group, a solvate thereof or a salt of this acid.

In a preferred embodiment of the invention, the 4-oxobutanoic acids are those of the formula (I) in which A and B are chosen from aryl groups.

Examples of aryl groups that may be mentioned include phenyl, α-naphthyl, β-naphthyl and fluorenyl groups.

The C_1-C_6 alkyl groups may be linear or branched. Examples that may be mentioned include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl and pentyl groups.

The C_1-C_6 alkoxy groups may also be linear or branched.

Examples that may be mentioned include methoxy, ethoxy, propoxy, isopropoxy, butoxy and isobutoxy groups.

The halogens may be chosen from fluorine, chlorine, bromine and iodine.

The present invention also includes the tautomeric forms of the compounds of the general formula (I), the enantiomers, diastereoisomers and epimers of these compounds, and also the solvates thereof.

Examples of salts of the compounds of the general formula (I) include pharmacologically acceptable salts, such as the sodium salts, potassium salts, magnesium salts, calcium salts, amine salts and other salts of the same type (aluminium, iron, bismuth, etc.).

In a preferred embodiment, the 4-oxobutanoic acids are chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid

- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,
- the solvates, enantiomers and salts of these acids.

Advantageously, the 4-oxobutanoic acid derivative is chosen from:

- (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (-)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid,
- the solvates and salts of these acids.

The compound that is most particularly preferred is 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid, its solvates, its enantiomers and its salts.

The compounds of the formula (I) were subjected to biological tests designed to reveal their anti-inflammatory activity. The *in vivo* activity of the compounds of the formula (I) was studied in an experimental model of inflammation in rats. Inflammatory oedema of the rat paw is induced by intradermal injection of carrageenan (1% V/V) into the hind paw of the rat. This oedema is measured by plethysmometry according to the method of Winter C.A. et al. (Proc. Soc. Exp. Biol. Med.; (1962); 111; 544-547). The substances with an anti-inflammatory effect bring about a reduction in the oedema thus created. Indomethacin is used as anti-inflammatory reference in the test.

The results show that the compounds of the formula (I) have anti-inflammatory properties *in vivo*. The treatment of inflammation may be performed preventively or curatively.

They may thus be used in this respect in the symptomatic treatment of painful conditions of mild to moderate intensity and/or febrile conditions, more particularly in diabetic neuropathy, polyarthritis, arthrosis, lumbago, traumatological pain and ORL inflammations.

The inflammation treated according to the invention may be associated with pathologies of insulin-resistant metabolic syndrome, with pathologies resulting from diabetes, for instance retinopathy, nephropathy, neuropathy, micro- and macro-angiopathy, hypertension or atherosclerosis. Specifically, diabetic patients with poor glycaemic control are liable to develop

atherosclerotic plaque infections associated with an inflammatory process [Endocr.; 2000, 6(3), 272-276]. This inflammation may also be associated with pathologies of central origin, for instance neurodegenerative diseases such as, especially, Alzheimer's disease or Parkinson's disease [Lancet; 2001, Aug 11, 358 (9280), 436 – J. Neuropathol. Exp. Neurol. 2001; Oct; 60 (10); 923].

The compounds of the invention may be presented, in combination with any suitable excipient, in any form that is suitable for enteral (more particularly oral) or parenteral administration, for example in the form of tablets, gel capsules, powders, sugar-coated tablets, or drinkable or injectable solutions. These suitable forms and suitable excipients are as defined in patent application WO 98/7681 filed by the Applicant.

The compounds of the formula (I) may be administered in daily doses of between about 1 and 400 mg to adults orally, or between 0.1 and 200 mg parenterally.

The examples below illustrate the present invention without, however, limiting it.

EXAMPLES

•Experimental data:

Animal model: Rat of Wistar type

Anti-inflammatory reference: indomethacin from the company Sigma

Control: 0.5 % methylcellulose hydrogel.

After fasting for one day, the volume of the right hind paw is measured [V paw]. The test compounds, the reference and the control are administered orally in a volume of 10 ml/kg. One hour after administration, oedema is induced by an intraplantar injection of 50 microlitres of carrageenan (1%, V/V) hydrogel into the right hind paw. The volume of this paw is measured three hours after inducing the oedema. The intensity of the oedema [V oedema] is evaluated by the difference in the volume of the paw, before and three hours after the injection of carrageenan.

The results are collated in the table below:

TEST OF CARRAGEENAN-INDUCED INFLAMMATORY OEDEMA

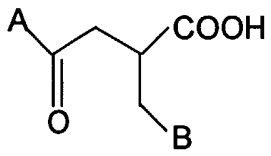
	V paw (ml)	V oedema (ml)	Reduction in oedema (%)
Controls	1.65	0.62	--
Indomethacin	1.65	0.20	- 67
P (30 mg)	1.57	0.42	- 32
P (100 mg)	1.67	0.11	- 83
P (300 mg)	1.71	0.17	- 73

P corresponds to (-)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid.

The experimental results show the anti-inflammatory effect of the compounds corresponding to the general formula (I).

CLAIMS

1. Use of at least one 4-oxobutanoic acid derivative of the formula (I) for the preparation of a medicament for treating inflammation, formula (I) being defined as follows:



(I)

in which the groups A and B are chosen, independently of each other, from:

- a mono-, bi- or tricyclic aryl group containing from 6 to 14 carbon atoms;
- a heteroaromatic group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl groups;
- an alkyl group containing from 1 to 14 carbon atoms;
- a cycloalkyl group containing from 5 to 8 carbon atoms;
- a saturated heterocyclic group chosen from tetrahydrofuryl, tetrahydropyranyl, piperidyl and pyrrolidinyl groups;

where the groups A and B may carry from 1 to 3 substituents chosen from a C_1-C_6 alkyl group, a C_1-C_6 alkoxy group, a C_6-C_{14} aryl group, a heteroaryl group chosen from pyridyl, pyrimidyl, pyrrolyl, furyl and thienyl, a (C_6-C_{14})aryl(C_1-C_6)alkyl group, a (C_6-C_{14})aryl(C_1-C_6)alkyl(C_6-C_{14})aryl group, a halogen or a trifluoromethyl, trifluoromethoxy, cyano, hydroxyl, nitro, amino, carboxyl, (C_1-C_6)-alkoxycarbonyl, carbamoyl, (C_1-C_6)alkylsulfonyl, sulfoamino, (C_1-C_6)alkylsulfonylamino, sulfamoyl or (C_1-C_6)alkylcarbonylamino group;

or two of the substituents form a methylenedioxy group, a solvate thereof or a salt of this acid.

2. Use according to Claim 1, characterised in that the 4-oxobutanoic acid derivative is chosen from:

- 2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid

- 2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- 2-cyclohexylmethyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-phenyl-4-oxobutanoic acid
- 2-(β-naphthylmethyl)-4-phenyl-4-oxobutanoic acid
- 2-benzyl-4-(β-naphthyl)-4-oxobutanoic acid
- 2-[(4-chlorophenyl)methyl]-4-(4-methoxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-(4-methylphenyl)-4-oxobutanoic acid
- 4-(4-fluorophenyl)-2-[(4-methoxyphenyl)methyl]-4-oxobutanoic acid
- 2-benzyl-4-(3,4-methylenedioxyphenyl)-4-oxobutanoic acid
- 2-benzyl-4-cyclohexyl-4-oxobutanoic acid
- 4-phenyl-2-[(tetrahydrofur-2-yl)methyl]-4-oxobutanoic acid,
- the solvates, enantiomers and salts of these acids.

3. Use according to Claim 1 or 2, characterised in that the compound of the formula (I) is chosen from:

- (-)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-methoxyphenyl)-4-oxobutanoic acid
- (-)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid
- (+)-2-benzyl-4-(4-fluorophenyl)-4-oxobutanoic acid,
- the solvates and salts of these acids.

4. Use according to one of the preceding claims, characterised in that the medicament is intended for the symptomatic treatment of painful conditions of mild to moderate intensity and/or febrile conditions.

5. Use according to one of Claims 1 to 3, characterised in that the medicament is intended for treating diabetic neuropathy, polyarthritis, arthrosis, lumbago, traumatological pain or ORL inflammations.

6. Use according to one of Claims 1 to 3, characterised in that the medicament is intended for treating inflammation associated with pathologies of insulin-resistant metabolic syndrome.

7. Use according to any one of Claims 1 to 3, characterised in that the medicament is intended for treating inflammation associated with pathologies resulting from diabetes, more particularly chosen from retinopathy, nephropathy, neuropathy, micro- or macro-angiopathy, hypertension and atherosclerosis.

8. Use according to any one of Claims 1 to 3, characterised in that the medicament is intended for treating inflammation associated with pathologies of central origin, more particularly chosen from neurodegenerative diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12357

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/192 A61K31/36 A61K31/341 A61P29/00 A61P43/00

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

B. FIELDS SEARCHED

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 67752 A (SANOFI SYNTHELABO ;CAILLE DOMINIQUE (FR)) 16 November 2000 (2000-11-16) the whole document	1,4-8
X	WO 00 06560 A (BRIEN PATRICK MICHAEL O ;WARNER LAMBERT CO (US); PICARD JOSEPH ARM) 10 February 2000 (2000-02-10) the whole document	1,4,5,8

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 January 2003	03/02/2003

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	Gac, G

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 200207 Derwent Publications Ltd., London, GB; AN 2001-570602 XP002203142 abstract & DATABASE CAPLUS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; voir les "IT" (termes d'indexation) : mitiglinide & WO 01 62295 A (FUNATSU MASAMI ;IWASAKI MASATO (JP); ODAKA HIROYUKI (JP); SUGIYAMA) 30 August 2001 (2001-08-30) ---	1,4-7
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN & JP 59 144717 A (MICROBIAL CHEM. RES. FOUND.), 18 August 1984 (1984-08-18) abstract ---	1
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/12357

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

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:

see FURTHER INFORMATION sheet PCT/ISA/210

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1,4-8 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 2 and 3.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/12357

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