



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 311/72, 307/80, C07C 235/34 A61K 31/355, 31/34, 31/16 // C07D 317/60, A61K 31/36	A3	(11) International Publication Number: WO 96/20187 (43) International Publication Date: 4 July 1996 (04.07.96)
(21) International Application Number: PCT/US95/16779 (22) International Filing Date: 21 December 1995 (21.12.95) (30) Priority Data: 08/362,718 23 December 1994 (23.12.94) US 08/472,445 7 June 1995 (07.06.95) US (60) Parent Applications or Grants (63) Related by Continuation US 08/362,718 (CIP) Filed on 23 December 1994 (23.12.94) US 08/472,445 (CIP) Filed on 7 June 1995 (07.06.95) (71) Applicant (for all designated States except US): ALCON LABORATORIES, INC. [US/US]; 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HELLBERG, Mark [US/US]; 5211 Overridge Drive, Arlington, TX 76017 (US). GRAFF, Gustav [US/US]; Route 4, Box 729E, Cle- burne, TX 76031 (US). GAMACHE, Daniel, A. [US/US];	5610 Hunterwood Lane, Arlington, TX 76017 (US). NIXON, Jon, C. [US/US]; 1616 Hastings Drive, Mansfield, TX 76063 (US). GARNER, William, H. [US/US]; 1615 Heather Lane, Southlake, TX 76092 (US). (74) Agents: MAYO, Michael, C. et al.; Alcon Laboratories, Inc., Patent Dept. Q-148, 6201 South Freeway, Fort Worth, TX 76134-2099 (US). (81) Designated States: AU, BR, CA, CN, FI, JP, KR, MX, NO, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> (88) Date of publication of the international search report: 12 December 1996 (12.12.96)	

(54) Title: ESTERS AND AMIDES OF NON-STEROIDAL ANTI-INFLAMMATORY CARBOXYLIC ACIDS WHICH MAY BE USED AS ANTI-OXIDANTS, 5-LIPOXYGENASE INHIBITORS AND NON-STEROIDAL ANTI-INFLAMMATORY PRODUCTS

(57) Abstract

The compounds of the present invention are of the formula (I): A-X-(CH₂)_n-Y-(CH₂)_m-Z wherein: A is a non-steroidal anti-inflammatory agent (NSAIA); A-X is an ester or amide linkage derived from the carboxylic acid moiety of the NSAIA, wherein X is O or NR; R is H, C₁-C₆ alkyl or C₃-C₆ cycloalkyl; Y, if present, is O, NR, C(R)₂, CH(OH) or S(O)_n; n is 2 to 4 and m is 1 to 4 when Y is O, NR, or S(O)_n; n is 0 to 4 and m is 0 to 4 when Y is C(R)₂ or is not present; n is 1 to 4 and m is 0 to 4 when Y is CH(OH); n' is 0 to 2; and Z is (a), (b), (c), (d) or (e) wherein: R' and R³ are H, C(O)R, C(O)N(R)₂, PO₃⁻, or SO₃⁻; R'' is H or C₁-C₆ alkyl; and R' and R³ together may form a ring having structure: (1) or (2); and provided that when Z is (e), X is not O. The compounds of the present invention also include pharmaceutically acceptable salts of the compounds of formula (I). Methods for treating inflammatory pathologies are disclosed. Particularly, the methods utilize pharmaceutical compositions containing certain compounds having an anti-inflammatory and anti-oxidant moiety covalently linked by an amide or ester bond. The compounds are useful in preventing and treating inflammatory disorders through several mechanisms.

(a)

(b)

(c)

(d)

(e)

(1)

(2)

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 95/16779

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D311/72 C07D307/80 C07C235/34 A61K31/355 A61K31/34
A61K31/16 //C07D317/60, A61K31/36

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 6 C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE WPI Section Ch, Week 9551 Derwent Publications Ltd., London, GB; AN 95-403834 XP002009524 "New alkyl-hydroxy-benzofuran and derivatives - are 5-lipoxygenase inhibitors useful in allergy or inflammation e.g. bronchial asthma, rheumatic disease, psoriasis" see abstract & WO,A,95 29906 (MEIJI MILK PRODUCTS CO., LTD.) 9 November 1995 see page 15	1-4, 22-24
Y	--- EP,A,0 183 869 (KURARAY CO., LTD.) 11 June 1986 see the whole document ---	1,22
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"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

15 October 1996

Date of mailing of the international search report

31.10.96

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/16779

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 279 867 (EFEKA FRIEDRICH & KAUFMANN GMBH & CO KG) 31 August 1988 see the whole document ---	1,22
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 5, May 1989, pages 1006-1020, XP002009522 HAMMOND M.L. ET AL.: "2,3-Dihydro-5-benzofuranols as antioxidant-based inhibitors of leukotriene biosynthesis" see the whole document ---	1,22
Y	EP,A,0 345 592 (TAKEDA CHEMICAL INDUSTRIES, LTD.) 13 December 1989 see the whole document ---	1,22
Y	JOURNAL OF MEDICINAL CHEMISTRY, vol. 33, no. 3, March 1990, pages 908-918, XP002009523 HAMMOND M.L. ET AL.: "Antioxidant-based inhibitors of leukotriene biosynthesis. The discovery of 6-[1-[2-(hydroxymethyl)phenyl]-1-propen-3- yl]-2,3-dihydro-5-benzofuranol, a potent topical antiinflammatory agent" see the whole document ---	1,22
Y	EP,A,0 380 367 (STAFFORD-MILLER LTD. & CONTINENTAL) 1 August 1990 see the whole document ---	1,22
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A	DATABASE WPI Week 8323 Derwent Publications Ltd., London, GB; AN 83-55213k XP002015865 "Indomethacin .alpha.-tocopherol ester preparation - by reacting indimethacin and .alpha.-tocopherol in an inert solvent" & JP,A,58 072 579 (SAWAI SEIYAKU K.K.) , 30 April 1983 see abstract ---	1,22
A	EP,A,0 387 771 (ONO PHARMACEUTICAL CO., LTD.) 19 September 1990 cited in the application see the whole document ---	1,22
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/16779

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 4, 18 February 1994, pages 526-541, XP002015864 PEARCE B.C. ET AL.: "Inhibitors of cholesterol biosynthesis. 2. Hypocholesterolemic and antioxidant activities of benzopyran and tetrahydronaphthalene analogues of the tocotrienols" see the whole document ---	1,22
P,A	EP,A,0 640 609 (ONO PHARMACEUTICAL CO., LTD.) 1 March 1995 see the whole document ---	1,22
P,A	US,A,5 424 321 (HELLBERG M.R. ET AL.) 13 June 1995 see the whole document ---	1,22
A	EP,A,0 241 043 (WARNER-LAMBERT COMPANY) 14 October 1987 see claims 1,8,11 ---	1-28
A	CHEMICAL & PHARMACEUTICAL BULLETIN , vol. 40, no. 2, 1992, pages 396-400, XP000570331 TSENG C.-F. ET AL.: "Inhibition of in vitro prostaglandin and leukotriene biosyntheses by cinnamoyl-.beta.-phenethylamine and N-acyldopamine derivatives" see page 398; table 2 -----	1-28

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 95/ 16779

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:
Although claims 29 to 36 are directed to a method of treatment of (diagnostic method practised on) 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. Claims 1-14(all part.), 16-21, and 22-28(all part.)
2. Claims 1-14(all part.), and 22-27(all part.)
3. Claims 1-14(all part.), 15, and 22-28(all part.)

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.:

1-14(all part.), 16-21 and 22-28(all part.)
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

Int: nal Application No

PCT/US 95/16779

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte: mal Application No

PCT/US 95/16779

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