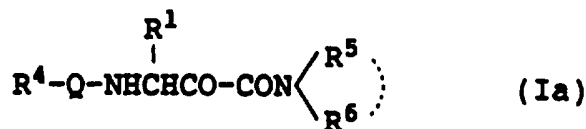




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>C07K 5/023, C07C 237/04, C07D 215/48</b>	<b>A3</b>	(11) International Publication Number: <b>WO 96/16079</b> (43) International Publication Date: 30 May 1996 (30.05.96)
<p>(21) International Application Number: PCT/JP95/02389</p> <p>(22) International Filing Date: 24 November 1995 (24.11.95)</p> <p>(30) Priority Data: 6/290132 24 November 1994 (24.11.94) JP</p> <p>(71) Applicant (for all designated States except US): TAKEDA CHEMICAL INDUSTRIES, LTD [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541 (JP).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): SOHDA, Takashi [JP/JP]; 27-20, Higashikanmaki 2-chome, Takatsuki-shi, Osaka 569 (JP). FUJISAWA, Yukio [JP/JP]; 1-31-104, Mikagenakamachi 4-chome, Higashinada-ku, Kobe-shi, Hyogo 658 (JP). YASUMA, Tsuneo [JP/JP]; 20-5, Takadacho, Ibaraki-shi, Osaka 567 (JP). MIZOGUCHI, Junji [JP/JP]; 18-D75-206, Tsukumodai 5-chome, Suita-shi, Osaka 565 (JP).</p> <p>(74) Agents: ASAHINA, Tadao et al.; Osaka Plant of Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532 (JP).</p>	<p>(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p> <p>(88) Date of publication of the international search report: 12 September 1996 (12.09.96)</p>	

(54) Title: ALPHA-KETOAMIDE DERIVATIVES AS CATHEPSIN L INHIBITOR



## (57) Abstract

The present invention relates to a cathepsin L inhibitor comprising a compound of general formula (Ia), wherein Q represents a direct bond or 1 or 2 amino acid residues that may be substituted; R<sup>1</sup> represents a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted; R<sup>4</sup> represents an acyl group or a carboxyl group that may be esterified and R<sup>5</sup> and R<sup>6</sup> independently represent a hydrogen atom or a hydrocarbon group or heterocyclic group that may be substituted or R<sup>5</sup> and R<sup>6</sup> may bind together to form a ring; or a salt thereof, which has strong bone resorption-suppressing action and is useful for preventing or treating osteoporosis.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<b>AT</b>	Austria	<b>GB</b>	United Kingdom	<b>MR</b>	Mauritania
<b>AU</b>	Australia	<b>GE</b>	Georgia	<b>MW</b>	Malawi
<b>BB</b>	Barbados	<b>GN</b>	Guinea	<b>NE</b>	Niger
<b>BE</b>	Belgium	<b>GR</b>	Greece	<b>NL</b>	Netherlands
<b>BF</b>	Burkina Faso	<b>HU</b>	Hungary	<b>NO</b>	Norway
<b>BG</b>	Bulgaria	<b>IE</b>	Ireland	<b>NZ</b>	New Zealand
<b>BJ</b>	Benin	<b>IT</b>	Italy	<b>PL</b>	Poland
<b>BR</b>	Brazil	<b>JP</b>	Japan	<b>PT</b>	Portugal
<b>BY</b>	Belarus	<b>KE</b>	Kenya	<b>RO</b>	Romania
<b>CA</b>	Canada	<b>KG</b>	Kyrgystan	<b>RU</b>	Russian Federation
<b>CF</b>	Central African Republic	<b>KP</b>	Democratic People's Republic of Korea	<b>SD</b>	Sudan
<b>CG</b>	Congo	<b>KR</b>	Republic of Korea	<b>SE</b>	Sweden
<b>CH</b>	Switzerland	<b>KZ</b>	Kazakhstan	<b>SI</b>	Slovenia
<b>CI</b>	Côte d'Ivoire	<b>LI</b>	Liechtenstein	<b>SK</b>	Slovakia
<b>CM</b>	Cameroon	<b>LK</b>	Sri Lanka	<b>SN</b>	Senegal
<b>CN</b>	China	<b>LU</b>	Luxembourg	<b>TD</b>	Chad
<b>CS</b>	Czechoslovakia	<b>LV</b>	Latvia	<b>TG</b>	Togo
<b>CZ</b>	Czech Republic	<b>MC</b>	Monaco	<b>TJ</b>	Tajikistan
<b>DE</b>	Germany	<b>MD</b>	Republic of Moldova	<b>TT</b>	Trinidad and Tobago
<b>DK</b>	Denmark	<b>MG</b>	Madagascar	<b>UA</b>	Ukraine
<b>ES</b>	Spain	<b>ML</b>	Mali	<b>US</b>	United States of America
<b>FI</b>	Finland	<b>MN</b>	Mongolia	<b>UZ</b>	Uzbekistan
<b>FR</b>	France			<b>VN</b>	Viet Nam
<b>GA</b>	Gabon				

INTERNATIONAL SEARCH REPORT

International Application No  
PCT/JP 95/02389

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07K5/023 C07C237/04 C07D215/48

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 C07K C07C 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.
X	WO,A,92 12140 (GEORGIA TECH RESEARCH CORPORATION) 23 July 1992	1-11,14, 16-20
Y	* pages 1-5; examples; table IV; claim 1 *	1-20
Y	--- EP,A,0 468 339 (NIPPON KAYAKU KABUSHIKI KAISHA) 29 January 1992 * claim 1; pages 4-11 *	1-13, 15-20
X	--- J. MED. CHEM., vol. 36, 1993, pages 3472-3480, XP000565670 LI, Z. ET AL.: "Peptide alpha-keto ester, alpha-keto amide, and alpha-keto acid inhibitors of calpains and other cysteine proteases"	1-6,10
Y	* page 3475, table II *	1-20
	--- -/--	

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

21 June 1996

Date of mailing of the international search report

02.08.96

Name and mailing address of the ISA

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

Authorized officer

Hermann, R

## INTERNATIONAL SEARCH REPORT

 International Application No  
 PCT/JP 95/02389

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARTHRITIS & RHEUMATISM, vol. 37, no. 2, 1 February 1994, pages 236-247, XP000566128 ESSER, R.E. ET AL.: "Cysteine proteinase inhibitors decrease articular cartilage and bone destruction in chronic inflammatory arthritis" * whole disclosure * ---	1-20
X	WO,A,94 08941 (CORVAS INTERNATIONAL, INC.) 28 April 1994 * claim 60 * ---	1,2,5-7
Y	* claim 60 * ---	1-7, 9-11, 16-20
X	WO,A,94 00095 (CORTEX PHARMACEUTICALS, INC.) 6 January 1994 cited in the application * pages 92-100 * ---	1-11, 16-20
Y	* pages 92-100 * ---	1-20
X	WO,A,92 11850 (CORTEX PHARMACEUTICALS, INC) 23 July 1992 * page 1, lines 13-24; page 40-48 * ---	1-11, 16-20 1-20
Y	* page 1, lines 13-24; page 40-48 * ---	1-20
Y	EP,A,0 603 769 (MITSUBISHI KASEI CORP.) 29 June 1994 * Summary; claim 1 * -----	1-20

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/02389

**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:
  
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:

see continuation-sheet

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

1. Claims: 12,13,15; claims 1-6, 8-11, and 16-20 partially: Compounds of claims 12-15 containing the motif  $-(\text{Leu,Val,Ile})-\text{Phe}-\text{CO}-\text{N}-$ , and an N-terminal cyclic alpha amino acid (e.g. the quinoline-2-carbonyl moiety), and corresponding subject-matter.
2. Claims: 1-7, 9-11, and 16-20 partially: Compounds containing the motif  $-(\text{Leu,Val,Ile})-\text{Phe}-\text{CO}-\text{N}-$ , and an N-terminal naphthalenesulfonyl moiety, and corresponding subject-matter.
3. Claims 1-11 and 16-20, all partially: other compounds of claims 1 and 6 wherein Ra and Rb are quinolyl or naphthyl, and corresponding subject-matter.
4. Claims 1-11 and 16-20, all partially: other compounds not yet covered by subjects 1-3, and corresponding subject-matter.

## INTERNATIONAL SEARCH REPORT

information on patent family members

Int. Application No  
PCT/JP 95/02389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9212140	23-07-92	AU-B- 654834	24-11-94
		AU-B- 9155391	17-08-92
		CA-A- 2098702	29-06-92
		EP-A- 0564561	13-10-93
		JP-T- 6504547	26-05-94
		US-A- 5257901	02-11-93
-----			
EP-A-0468339	29-01-92	JP-A- 4211648	03-08-92
		US-A- 5221752	22-06-93
		JP-A- 5221967	31-08-93
-----			
WO-A-9408941	28-04-94	US-A- 5371072	06-12-94
		AU-B- 5408194	09-05-94
		EP-A- 0664786	02-08-95
		JP-T- 8502493	19-03-96
-----			
WO-A-9400095	06-01-94	AU-B- 4544993	24-01-94
		CA-A- 2138124	06-01-94
		EP-A- 0650368	03-05-95
-----			
WO-A-9211850	23-07-92	AU-B- 667463	28-03-96
		AU-B- 9152791	17-08-92
		CA-A- 2098609	29-06-92
		EP-A- 0564552	13-10-93
		JP-T- 6504061	12-05-94
		US-A- 5444042	22-08-95
-----			
EP-A-0603769	29-06-94	CA-A- 2111931	26-06-94
		JP-A- 7070058	14-03-95
		US-A- 5422359	06-06-95
-----			