



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/023, A61K 38/05	A3	(11) International Publication Number: WO 98/24804 (43) International Publication Date: 11 June 1998 (11.06.98)
(21) International Application Number: PCT/US97/22355 (22) International Filing Date: 5 December 1997 (05.12.97) (30) Priority Data: 60/032,129 6 December 1996 (06.12.96) US 60/041,938 4 April 1997 (04.04.97) US 60/050,796 26 June 1997 (26.06.97) US (71) Applicant (for all designated States except US): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): GOLEC, Julian, M., C. [GB/GB]; 8 Manor Farm, Chapel Road, Ashbury, Swindon, Wiltshire SN6 8LS (GB). LAUFFER, David, J. [US/US]; 254 Taylor Road, Stow, MA 01775 (US). LIVINGSTON, David, J. [US/US]; 20 Madison Avenue, Newtonville, MA 02160 (US). MULLICAN, Michael, D. [US/US]; 110 Parker Road, Needham, MA 02194 (US). NYCE, Philip, L. [US/US]; 18 Prospect Street, Millbury, MA 01527 (US). ROBIDOUX, Andrea, L., C. [US/US]; 180 Salem Street, Andover, MA 01810 (US). WANNAMAKER, Marion, W. [US/US]; 375 Harvard Road, Stow, MA 01775 (US).		(74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al. (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, 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). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 3 September 1998 (03.09.98)
(54) Title: INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYME (57) Abstract The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme ("ICE"). This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1"), apoptosis-, interferon-γ inducing factor- (IGIF), or interferon-γ- ("IFN-γ") mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting ICE activity and decreasing IGIF production and IFN-γ production and methods for treating interleukin-1, apoptosis- and interferon-γ- mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22355

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07K5/023 A61K38/05

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

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 95 35308 A (VERTEX PHARMA) 28 December 1995	1-41
Y	See especially page 40, formula w, page 57, formula o3, page 62, formula w1, page 88-89, page 244-256; claims 80, 81, 84, 85, 94-101, 117	1, 2, 5-7, 9, 12-41
P, Y	--- DOLLE R E ET AL: "PYRIDAZINODIAZEPINES AS A HIGH-AFFINITY, P2-P3 PEPTIDOMIMETIC CLASS OF INTERLEUKIN-1BETA-CONVERTING ENZYME INHIBITOR" JOURNAL OF MEDICINAL CHEMISTRY, vol. 40, no. 13, 20 June 1997, pages 1941-1946, XP002039102 See especially Chart 1 ---	1, 2, 5-7, 9, 12-41

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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 :

"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

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"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

10 March 1998

Date of mailing of the international search report

15. 07. 1998

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 97/22355

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 22619 A (VERTEX PHARMA) 26 June 1997 See especially claims 1-3 ---	1-41
P,X	JP 09 295 996 A (TAKEDA CHEMICAL INDUSTRIES) 18 November 1997 see the whole document & DATABASE WPI Derwent Publications Ltd., London, GB; AN 98-046961 see abstract -----	1,2, 5-10, 12-41
T		

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/22355

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 additional 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.:

1, 2, 9-12a(complete); 5-8, 12b-41(partial)

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: 1,2,9-12a(complete)5-8,12b-41(partially)

Compounds containing the substructure III,their preparation,
pharmaceutical compositions and use.

2. Claims: 3,4(complete),5-8,12b-41(partially)

Compounds containing the substructure IV, their peparation,
pharmaceutical compositions and use.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 97/22355

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9535308 A	28-12-95	US 5756466 A	26-05-98
		US 5656627 A	12-08-97
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		BG 101130 A	29-08-97
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		EP 0784628 A	23-07-97
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JP 9295996 A	18-11-97	NONE	
