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(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, EC, 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, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

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Published:
— *with international search report*

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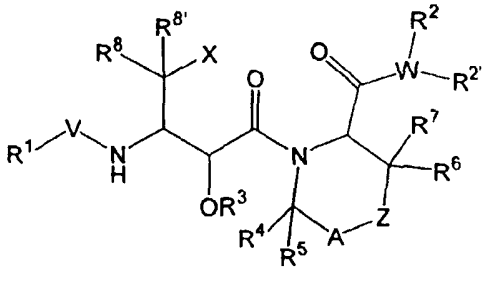
[Continued on next page]

(54) Title: HIV PROTEASE INHIBITORS, COMPOSITIONS CONTAINING THE SAME, THEIR PHARMACEUTICAL USES AND MATERIALS FOR THEIR SYNTHESIS



(I)

(57) Abstract: Compounds of Formula (I), where the formula variables are as defined herein, are disclosed that advantageously inhibit or block the biological activity of the HIV protease. These compounds, as well as pharmaceutical compositions containing these compounds, are useful for treating patients or hosts infected with the HIV virus. Intermediates and synthetic methods for preparing such compounds are also described.

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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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/18717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/06 A61K31/426 C07D401/12 C07D417/12 C07D207/16
C07D265/06 C07D211/60 A61P31/18

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)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 706 794 A (JAPAN ENERGY CORP) 17 April 1996 (1996-04-17) the whole document ---	1,2,7, 31-37,43
X	EP 0 751 145 A (JAPAN ENERGY CORP) 2 January 1997 (1997-01-02) cited in the application the whole document ---	1,2,7, 31-37,43
X	KISO ET AL.: "KNI-577, a potent small-sized HIV protease inhibitor based on the dipeptide containing the hydroxymethylcarbonyl isostere as an ideal transition-state mimic" ARCH. PHARM. PHARM. MED. CHEM., vol. 331, 1998, pages 87-89, XP002212194 the whole document --- -/--	1,2,7, 31-37,43

[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
18 November 2002	09.12.02

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	Lauro, P

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

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	MIMOTO T ET AL: "Structure-Activity Relationship of Small-Sized HIV Protease Inhibitors Containing Allophenylnorstatine" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 42, no. 10, 24 April 1999 (1999-04-24), pages 1789-1802, XP002192452 ISSN: 0022-2623 cited in the application the whole document	1,2,7, 31-37,43
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Y	table II	9,12, 14-18, 23,24, 27-30
X	SAKURAI M ET AL: "STRUCTURE-ACTIVITY RELATIONSHIPS OF HIV-1 PR INHIBITORS CONTAINING AHPBA" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 2, no. 8, 1994, pages 807-825, XP000653621 ISSN: 0968-0896 tables 2,3	1,2,7, 11,13, 22,25,26
Y	page 811	9,12, 14-18, 23,24, 27-30

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	VAN-DUC LE: "Structure-Activity studies of FIV and HIV Protease Inhibitors containing Allophenylnorstatine" BIOORG.MED. CHEM., vol. 9, February 2001 (2001-02), pages 1185-95, XP002221131 the whole document	1,2,7, 13,25,26
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 490 667 A (NIPPON MINING CO) 17 June 1992 (1992-06-17) the whole document	10,11, 13, 19-22, 25,26
X	WO 93 13066 A (SYNTEX INC) 8 July 1993 (1993-07-08) the whole document	10,11, 13, 19-22, 25,26
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X	DEMANGE L ET AL: "Practical Synthesis of Boc and Fmoc Protected 4-Fluoro and 4-Difluoroprolines from Trans-4-Hydroxyproline" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 39, no. 10, 5 March 1998 (1998-03-05), pages 1169-1172, XP004109146 ISSN: 0040-4039 the whole document	42

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	FALORNI M ET AL: "Optically Active 4-Oxaproline Derivatives: New Useful Chiral Synthons Derived from Serine and Threonine" TETRAHEDRON: ASYMMETRY, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 6, no. 1, 1995, pages 287-294, XP004048523 ISSN: 0957-4166 the whole document	42

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/18717

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 claims 38-41 are 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. [X] Claims Nos.: 1(part),2-8,31-37(part),43(part)
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:

see additional sheet

1. [X] 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.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1(part),2-8,31-37(part),43(part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of claim 1 due to the extereme broadness of the claim. So many documents were retrieved that it is impossible to determine which parts of the claim(s) may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, only a small number of the documents which have been found is cited.

Prodrug forms and pharmaceutically active metabolites have not been searched.

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1(part),2-8,31-37(part),43(part)

   Compounds of formula (I-A) and their pharmaceutical use

2. Claims: 1(part),9,15-18,31-37(part),43(part)

   Compounds of formula (I-B) and their pharmaceutical use

3. Claims: 1(part),10,19-21,31-37(part),43(part)

   Compounds of formula (I-C) and their pharmaceutical use

4. Claims: 1(part),11,22,31-37(part),43(part)

   Compounds of formula (I-D) and their pharmaceutical use

5. Claims: 1(part),12,23-24,31-37(part),43(part)

   Compounds of formula (I-E) and their pharmaceutical use

6. Claims: 1(part),13,25-26,31-37(part),43(part)

   Compounds of formula (I-F) and their pharmaceutical use

7. Claims: 1(part),14,27-30,31-37(part),43(part)

   Compounds of formula (I-G) and their pharmaceutical use

8. Claim : 42

   5-membered 2-carboxyl substituted nitrogen-containing compounds in which the ring nitrogen is substituted by a t-butyloxycarbonyl

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/18717

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