

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
5 June 2003 (05.06.2003)

PCT

(10) International Publication Number
WO 2003/045977 A3

- (51) International Patent Classification⁷: **A61K 38/05**, 38/04, 31/69, 31/675, 31/401, C07K 5/04, 5/06, C07F 9/572, 5/04, C07D 207/12
- (21) International Application Number: PCT/US2002/038053
- (22) International Filing Date: 26 November 2002 (26.11.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/333,519 26 November 2001 (26.11.2001) US
60/405,530 23 August 2002 (23.08.2002) US
- (71) Applicant (for all designated States except US): **TRUSTEES OF TUFTS COLLEGE** [US/US]; Ballou Hall, Medford, MA 02155 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **BACHOVCHIN, William, W.** [US/US]; 7 Warwick Street, Melrose, MA 02176 (US).
- (74) Agents: **VINCENT, Matthew, P.** et al.; Ropes & Gray, One International Place, Boston, MA 02110-2624 (US).
- (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, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 13 May 2004
- 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.*

(54) Title: Peptidomimetic Inhibitors of Post-Proline Cleaving Enzymes

(57) Abstract: The present invention relates to inhibitors of post-proline cleaving enzymes, such as inhibitors of dipeptidyl peptidase IV, as well as pharmaceutical compositions thereof, and methods for using such inhibitors. In particular, the inhibitors of the present invention are improved over those in the prior art by selection of particular classes of sidechains in the P1 and/or P2 position of the inhibitor. The compounds of the present invention can have a better therapeutic index, owing in part to reduced toxicity and/or improved specificity for the targeted protease.



WO 2003/045977 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/38053

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 38/05, 38/04, 31/69, 31/675, 31/401; C07K 5/04, 5/06; C07F 9/572, 5/04; C07D 207/12
 US CL : 514/2, 7, 19, 84,91, 217.11, 210.17, 330, 423, 3; 530/300; 540/541, 542, 607; 546/13, 21,226

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)

U.S. : 514/2, 7, 19, 84,91, 217.11, 210.17, 330, 423, 3; 530/300; 540/541, 542, 607; 546/13, 21,226 548;412,405, 533,953

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 practicable, search terms used)
WEST**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COUTTS, et al Structure-Activity Relationships of Boronic acid Inhibitors of Dipeptidase IV, Journal of Med. Chem, 1996, 39 2087-2094 See P. 2092, Column 2, and P. 2093, Column 1	1, 5-27
X	JOLLE, et al, Pristinamycin, Bull. Soc. Chim France (1965) 8, 2252-9 Chemical Abstracts 63:72425 See the structure in the abstract.	1, 5-27
X	US 2001/0020006 A1(DEMUTH et al) 06 September 2001 (06.09.2001) See Column 1, P. 4	1, 5-27
X	US 5,543,396 A (POWERS et al) 06 August, 1996 (06.08.1996) See examples 25-29	1, 5-27
X	US 5,585,390 A (DUFLOS, et al) 17 December 1996 (17.12.1996) See Column 7, lines 10-15	1, 5-27

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:	"T"
"A" document defining the general state of the art which is not considered to be of particular relevance	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
"E" earlier application or patent published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

12 January 2004 (12.01.2004)

Date of mailing of the international

05 MAR 2004

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
 Commissioner for Patents
 P.O. Box 1450
 Alexandria, Virginia 22313-1450

Facsimile No. (703)305-3230

Authorized officer

Edward C Ward

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/38053

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. Claim 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. Claim 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:
Please 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.: 1, and 5 to 27

- Remark on Protest**
- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group 1, claim(s) 1, and 5 to 27, drawn to C end hetero ring containing peptides.

Group 2, claim(s) 2 and 5 to 27, drawn to no hetero ring containing peptides.

Group 3, claim(s) 3 and 5 to 27 drawn to N side hetero ring containing peptides.

Group 4, claim(s) 4 and 5 to 27, drawn to two hetero ring containing peptides.

Group 1 has the hetero ring on the C side of the peptide. Group 2 has no hetero ring. Group 3 has the hetero ring on the N side of the peptide, and Group 4 has two hetero rings. The inventions listed as Groups 1 to 4 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: There are 4 distinct peptide structures, each requiring separate search because of the differences in the peptide sequences..