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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 February 2004 (12.02.2004)

PCT

(10) International Publication Number
WO 2004/012732 A3

(51) International Patent Classification[7]: A61K 31/4015, C07D 207/46, 263/14, A61K 38/06, A61P 9/10

(21) International Application Number: PCT/EP2003/008495

(22) International Filing Date: 31 July 2003 (31.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02017234.2 31 July 2002 (31.07.2002) EP

(71) Applicant *(for all designated States except US)*: **CHARITÉ-UNIVERSITÄTSMEDIZIN BERLIN** [DE/DE]; Schumannstrasse 20/21, 10117 berlin (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **STANGL, Verena** [DE/DE]; Nassauische Strasse 7-8, 10717 Berlin (DE). **STANGL, Karl** [DE/DE]; Nassauische Strasse 7-8, 10717 Berlin (DE). **LORENZ, Mario** [DE/DE]; Jablonskistrasse 5, 10405 Berlin (DE).

(74) Agents: **KRAUSS, Jan, B.** et al.; Boehmert & Boehmert, Pettenkoferstrasse 20-22, 80336 München (DE).

(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, SC, SD, SE, SG, 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, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, 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: 29 April 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: USE OF A PROTEASOME INHIBITOR IN THE TREATMENT OF ENDOTHELIAL DYSFUNCTION AND/OR IN A LOW-DOSE PROTEASOME INHIBITOR THERAPY

(57) Abstract: The present invention relates to the use of a proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases associated with endothelial dysfunction. The present invention also relates to the use of a proteasome inhibitor as a low-dose treatment.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08495

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4015 C07D207/46 C07D263/14 A61K38/06 A61P9/10

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 A61K 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)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/047540 A (BETH ISRAEL HOSPITAL) 5 July 2001 (2001-07-05) *cf. abstract, page 7, lines 19-25, page 8, line 23 bridging with page 9, line 24, experiment 2 on pp. 46/47, claims 1/4/5*	1-10, 13-24
X	WO 99/09006 A (BEHNKE MARK ;ROUSH WILLIAM (US); PLAMONDON LOUIS (US); SOUCY FRANC) 25 February 1999 (1999-02-25) *cf. abstract, page 9, line 15 bridging with page 10, line 2, page 31, line 2, page 41, lines 3-9, example 15 on page 67ff., page 69, lines 1-5, claims 71/72*	1-10, 13-24

☐ 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	Date of mailing of the international search report
17 December 2003	12 03. 2004

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	Stoltner, A

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08495

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.: 1-2
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. ☐ 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.:
1-10, 13-24 (part)

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

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

1. claims: 1-10, 13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

a) naturally occurring proteasome inhibitors comprising peptide derivatives which have a C-terminal epoxy keton structure, beta-lacton-derivatives, aclacinomycin A, lactacystin, clastolactacystin.

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2. claims: 1-10, 13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

b) synthetic proteasome inhibitors comprising: modified peptide aldehydes such as N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (MG132), or the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (PS1).

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3. claims: 1-10,13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

c) peptides comprising: an alpha,beta-epoxyketone-structure, vinyl-sulfones such as carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon or 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS).

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4. claims: 1-10, 13-24 (PART)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

d) Glyoxal- or boric acid residues such as pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)2 and dipeptidyl-boric-acid derivatives.

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5. claims: 1-10,13-24 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

e) Pinacol-esters such as:
benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacolester.

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6. claims: 11,25 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

f) a proteasome inhibitor interfering with proteasomal gene expression, selected from a group comprising antisense RNA, double stranded RNA and oligonucleotides hybridising with a DNA sequence encoding at least one component of the proteasome complex.

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7. claims: 12,26 (PART)

Use of at least on proteasome inhibitor for the manufacture of a medicament for the prevention, onset therapy, acute therapy and/or regression of diseases "associated with endothelial dysfunction", wherein the proteasome inhibitor is selected from a group comprising:

g) a proteasome inhibitor interfering with a proteasomal gene expression selected from a group comprising a knock out construct

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2

Present claims 1-26 relate to an extremely large number of possible compounds. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear namely those compounds recited in the examples and closely related homologous compounds mentioned in the claims 6 and 7. Moreover, the claims covering all compounds having the characteristic or property of being useful in the treatment/therapy of "diseases associated with endothelial dysfunction" only find support within the meaning of Article 6 PCT within the meaning of Article 5 PCT for only a very limited number of such compounds (MG132). In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

The applicant's attention is drawn to the fact that 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. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08495

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