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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 January 2014 (09.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/008204 A3

(51) International Patent Classification:
C07D 225/02 (2006.01) *C07C 49/307* (2006.01)
C07D 245/02 (2006.01) *A61P 35/00* (2006.01)
C07D 285/00 (2006.01) *A61K 31/33* (2006.01)

(21) International Application Number:
PCT/US2013/048966

(22) International Filing Date:
1 July 2013 (01.07.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/667,396 2 July 2012 (02.07.2012) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(88) Date of publication of the international search report:
27 February 2014

(54) Title: STRUCTURES OF PROTEASOME INHIBITORS AND METHODS FOR SYNTHESIZING AND USE THEREOF

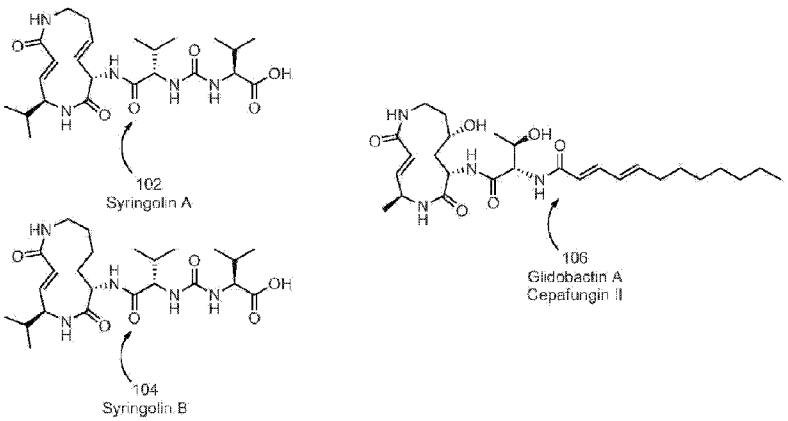


FIG. 1

(57) Abstract: Disclosed herein are novel structures of proteasome inhibitors and methods for synthesizing and use thereof, including novel structures of proteasome inhibitors, such as syrbactins and its analogs, and methods for synthesizing them and using them for effective proteasome inhibition.

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INTERNATIONAL SEARCH REPORT

International application No.
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A. CLASSIFICATION OF SUBJECT MATTER
(see extra sheet)

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)
C07D 225/02, 245/02, 285/00, C07C 49/307, A61P 35/00, A61K 31/33, C07K 5/12, C07C 49/547, 49/587, C07K 5/02

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)
STN, DWPI, RUPAT, EAPO, Esp@cenet, PAJ, USPTO, CIPO, DEPATIS, PCT Online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	US 2010/0022767 A1 (MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.) 28.01.2010	
X		1-10, 13-17, 20-21, 23-24, 30, 33-42, 45-49, 52, 53, 55, 56, 62, 65-74, 77-81, 84-85, 87, 88, 94, 97-106, 109-113, 116-117, 119, 120, 126, 129-138, 141-145, 148-149, 151, 152, 158, 161-170, 173-177, 180-181, 184, 183, 190, 309-311, 313-324
Y		231-233, 235-236, 239-246, 248, 251-253, 256-264, 265, 297, 352, 364, 376, 422
A		193-229, 234, 266-296, 298-308, 325-351, 353-363, 365-375, 377-399, 423-436

[X] Further documents are listed in the continuation of Box C. [ ] See patent family 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
30 August 2013 (30.08.2013)	05 December 2013 (05.12.2013)
Name and mailing address of the ISA/ FIPS Russia, 123995, Moscow, G-59, GSP-5, Berezhkovskaya nab., 30-1 Facsimile No. +7 (499) 243-33-37	Authorized officer E. Guseva Telephone No. (495)531-64-81

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2013/048966

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 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.: 11-12, 18-19, 22, 43-44, 50-51, 54, 75-76, 82-83, 86, 107-108, 114-115, 118, 139-140, 146-147, 150, 171-172, 178-179, 182, 312 (all completely), 1-10, 13-17, 20-21, 23-42, 45-49, 52-53, 55-74, 77-81, 84-85, 87-106, 109-113, 116-117, 119-138, 141-145, 148-149, 151-170, 173-177, 180-181, 183-311, 313-399, 422-436 (all partially)
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:

Claims 11-12, 22, 43-44, 54, 75-76, 86, 107-108, 118, 139-140, 150, 171-172, 182 are unclear, since it is specified that R^{10} and R^{11} or R^{12} and R^{13} form rings consist of alkyl and arylalkyl, but alkyl is not a ring.
Claim 312 is unclear, since the chemical formula is not specified.
Claims 405-421 are unclear, since the chemical structure of the ligand intermediate is not clear.
The search and examination for Claims 1-10, 13-17, 20-21, 23-42, 45-49, 52-53, 55-74, 77-81, 84-85, 87-106, 109-113, 116-117, 119-138, 141-145, 148-149, 151-170, 173-177, 180-181, 183-399, 422-436 have been restricted to compounds having 12-member cyclic structures, the use and synthesis thereof.
The search and examination for methods of Claims 193-311, 313-436 have been restricted to those depicted on figures 1/32-32/32.
Hence, the international search and examination have not been carried out for Claims 11-12, 18-19, 22, 43-44, 50-51, 54, 75-76, 82-83, 86, 107-108, 114-115, 118, 139-140, 146-147, 150, 171-172, 178-179, 182, 312.

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 No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The present international application lacks unity a priori within the meaning of Rule 13 PCT. Claims of the invention comprise 2 groups of inventions, which are not so linked as to form a single inventive concept.
The first group of inventions comprises Claims 1-399, 422-436 and relates to the proteasome inhibitors structures, the use and the synthesis thereof.
The second group of inventions comprises Claims 400-421 and relates to the synthesis of ligand intermediates.

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 additional fees, this Authority did not invite payment of additional fees.

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 and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2013/048966

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/081731 A2 (MAX-PLANCK-GESELLSCHAFT ZUR FORDERUNG DER WISSENSCHAFTEN E.V.) 22.07.2010, abstract, p.p. 22-23, 29-80, fig. 1/2-2/2	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 24, 30, 56, 62, 88, 94, 120, 126, 216, 152, 158, 184, 190, 309-311, 313-324, 405-414
Y		231-233, 235-236, 239-246, 248, 251-253, 256-264, 265, 297, 352, 364, 376, 422
X	WO 2011/069045 A2 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA) 09.06.2011, p.p. 6-10, 31-35	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 24, 30-32, 56, 62-64, 88, 94-96, 120, 126-128, 152, 158-160, 184, 190-192, 230, 237-238, 247, 249-250, 254-255
Y		231-233, 235-236, 239-246, 248, 251-253, 256-264, 400-404, 265, 297, 352, 364, 376, 422
X	WO 2009/065090 A2 (UNIVERSITY OF HAWAII) 22.05.2009, abstract, p.p. 52-54	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 24-31, 56-63, 88-95, 120-127, 152-159, 184-191.
X	EP 0437244 A1 (BRISTOL-MYERS SQUIBB COMPANY) 17.07.91, p.p. 2-3	1-10, 13-16, 21, 23, 33-42, 45-48, 53, 55, 65-74, 77-80, 85, 87, 97-106, 109-112, 117, 119, 129-138, 141-145, 149, 151, 161-170, 173-177, 181, 183 , 30, 62, 94, 126, 158, 190
X	US 472047 A (BRISTOL-MEYERS COMPANY) 03.05.1988, col. 1-14	1-10, 13-16, 21, 23, 33-42, 45-48, 53, 55, 65-74, 77-80, 85, 87, 97-106, 109-112, 117, 119, 129-138, 141-145, 149, 151, 161-170, 173-177, 181, 183 , 30, 62, 94, 126, 158, 190
Y		417-421

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 2013/048966

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JUN FU et al. Full-length RecE enhances linear-linear homologous recombination and facilitates direct cloning for bioprospecting. Nature Biotechnology, 2012, 30(5), 440-446, especially p. 444	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 30, 62, 94, 126, 158, 190
X	MASAHISA OKA et al. Chemical Modification of the Antitumor Antibiotic Glidobactin. The Journal of Antibiotics, 1988, 41(12), pp. 1812-1822	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 30, 62, 94, 126, 158, 190
X	NICOLAOU K. C. et al. A New Method for the One-Step Synthesis of α,β-Unsaturated Carbonyl Systems from Saturated Alcohols and Carbonyl Compounds. Journal of the American Chemical Society, 2000, 122(31), 7596-7597, table 1	1-10, 33-42, 65-74, 97-106, 129-138, 161-170
X	US 4393245 A (BASF AKTIENGESELLSCHAFT) 12.07.1983, examples 3, 4	1-10, 33-42, 65-74, 97-106, 129-138, 161-170
X	US 3754036 A (INTERNATIONAL FLAVORS & FRAGRANCES INC.) 21.08.1973, col. 4-14	1-10, 33-42, 65-74, 97-106, 129-138, 161-170
X	CLERC, Jerome et al. Convergent Synthesis and Biological Evaluation of Syringolin A and Derivatives as Eukaryotic 20S Proteasome Inhibitors. Eur. J. Org. Chem., 2010, pp. 3991-4003	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 415-416
X	PIRRUNG, Michael C. et al. Total Synthesis of Syringolin A. Organic Letters, 2010, 12(10), pp. 2402-2405	1-10, 13-17, 20-21, 23, 33-42, 45-49, 52, 53, 55, 65-74, 77-81, 84-85, 87, 97-106, 109-113, 116-117, 119, 129-138, 141-145, 148-149, 151, 161-170, 173-177, 180-181, 183, 247-264
Y		231-233, 235-236, 239-246, 265, 297, 352, 364, 376, 422
Y	[online] DB CAS, alanine tret-butyl ester (CAS 21691-50-9), methyl-(2S)-2-isocyanatopropanoate (CAS 30293-82-4)	400-404

INTERNATIONAL SEARCH REPORT
Classification of subject matter

International application No.
PCT/US 2013/048966

C07D 225/02 *(2006.01)*
C07D 245/02 *(2006.01)*
C07D 285/00 *(2006.01)*
C07C 49/307 *(2006.01)*
A61P 35/00 *(2006.01)*
A61K 31/33 *(2006.01)*