

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

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

07 March 2019 (07.03.2019)



(10) International Publication Number

WO 2019/043176 A3

(51) International Patent Classification:

A61K 45/06 (2006.01) A61K 31/513 (2006.01)
A61K 31/4025 (2006.01) A61P 35/00 (2006.01)

(21) International Application Number:

PCT/EP2018/073504

(22) International Filing Date:

31 August 2018 (31.08.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

17188794.6 31 August 2017 (31.08.2017) EP

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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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, SA, 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, ST, 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))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

11 April 2019 (11.04.2019)

(54) Title: HDAC INHIBITOR IN COMBINATION WITH ANTIMETABOLITE AGENT FOR CANCER THERAPY

(57) Abstract: The invention relates to methods, compositions and uses for the treatment of cancer comprising the administration of an HDAC inhibitor for the treatment of cancer in combination with an antimetabolite agent.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/073504

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K45/06 A61K31/4025 A61K31/513 A61P35/00 ADD.								
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) 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 practicable, search terms used) EPO-Internal, BIOSIS, CHEM ABS Data, COMPENDEX, EMBASE, INSPEC, WPI Data								
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>Y</td> <td> SHUAI GAO ET AL: "Preclinical and Clinical Studies of Chidamide (CS055/HBI-8000), An Orally Available Subtype-selective HDAC Inhibitor for Cancer Therapy", ANTI-CANCER AGENTS IN MEDICINAL CHEMISTRY, vol. 17, no. 6, 5 June 2017 (2017-06-05), XP055530087, NL ISSN: 1871-5206, DOI: 10.2174/1871520616666160901150427 paragraphs [0003], [5.1.2], [5.2.1] - [5.2.4] ----- -/-- </td> <td>1-13</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	SHUAI GAO ET AL: "Preclinical and Clinical Studies of Chidamide (CS055/HBI-8000), An Orally Available Subtype-selective HDAC Inhibitor for Cancer Therapy", ANTI-CANCER AGENTS IN MEDICINAL CHEMISTRY, vol. 17, no. 6, 5 June 2017 (2017-06-05), XP055530087, NL ISSN: 1871-5206, DOI: 10.2174/1871520616666160901150427 paragraphs [0003], [5.1.2], [5.2.1] - [5.2.4] ----- -/--	1-13
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Y	SHUAI GAO ET AL: "Preclinical and Clinical Studies of Chidamide (CS055/HBI-8000), An Orally Available Subtype-selective HDAC Inhibitor for Cancer Therapy", ANTI-CANCER AGENTS IN MEDICINAL CHEMISTRY, vol. 17, no. 6, 5 June 2017 (2017-06-05), XP055530087, NL ISSN: 1871-5206, DOI: 10.2174/1871520616666160901150427 paragraphs [0003], [5.1.2], [5.2.1] - [5.2.4] ----- -/--	1-13						
☒ 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 application or patent 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 December 2018		25/02/2019						
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Bareyt, Sébastien						

INTERNATIONAL SEARCH REPORT

International application No.
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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.:
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 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:

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 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.:

1-13(partially)

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/EP2018/073504

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "4SC-201 (Resminostat) in Advanced Colorectal Carcinoma", 1 February 2015 (2015-02-01), pages 1-8, XP055530023, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NC T01277406 [retrieved on 2018-12-04]	1-5,8-13
Y	page 4, line 13	1-13
Y	----- NOEMI ARRIGHETTI ET AL: "Drug Combinations with HDAC Inhibitors in Antitumor Therapy", CRITICAL REVIEWS IN ONCOGENESIS, vol. 20, no. 1-2, 1 January 2015 (2015-01-01), pages 83-117, XP055369440, ISSN: 0893-9675, DOI: 10.1615/CritRevOncog.2014012378 paragraph [B.1.d]	1-13
Y	----- SHUICHI IWAHASHI ET AL: "Effects of Valproic Acid in Combination with S-1 on Advanced Pancreatobiliary Tract Cancers: Clinical Study Phases I/II", ANTICANCER RESEARCH, vol. 34, no. 9, 1 September 2014 (2014-09-01), pages 5187-5192, XP055530060, page 5187, right-hand column, line 3 last, last paragraph	1-13
Y	----- RINTARO NORO ET AL: "Histone deacetylase inhibitor enhances sensitivity of non-small-cell lung cancer cells to 5-FU/S-1 via down-regulation of thymidylate synthase expression and up-regulation of p21waf1/cip1 expression", CANCER SCIENCE, vol. 101, no. 6, 10 March 2010 (2010-03-10), pages 1424-1430, XP055530053, JP ISSN: 1347-9032, DOI: 10.1111/j.1349-7006.2010.01559.x page 1426 ----- -/--	1-13

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/073504

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ELENA DI GENNARO ET AL: "Modulation of thymidilate synthase and p53 expression by HDAC inhibitor vorinostat resulted in synergistic antitumor effect in combination with 5FU or Raltitrexed", CANCER BIOLOGY & THERAPY, vol. 8, no. 9, 1 May 2009 (2009-05-01), pages 782-791, XP055530078, US ISSN: 1538-4047, DOI: 10.4161/cbt.8.9.8118 abstract -----	1-13
X,P	CHIGUZA MORIZANE ET AL: "Phase I study of resminostat, an HDAC inhibitor, combined with S-1 in patients with pre-treated biliary tract or pancreatic cancer", INVESTIGATIONAL NEW DRUGS., vol. 28, no. Suppl. 5, 1 September 2017 (2017-09-01), pages 1-9, XP055530038, US ISSN: 0167-6997, DOI: 10.1093/annonc/mdx369.130 the whole document -----	1-13

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-13(partially)

relates to combination of at least resminostat and a fluoropyrimidine derivative.

2. claims: 1-4, 8-13(all partially)

relates to compositions containing resminostat but not a fluoropyrimidine derivative.

3. claims: 1, 2, 5-13(all partially)

relates to compositions containing a fluoropyrimidine derivative but not resminostat

4. claims: 1, 2, 8-13(all partially)

relates to compositions containing neither resminostat nor a fluoropyrimidine derivative
