



(43) International Publication Date
22 June 2017 (22.06.2017)

(10) International Publication Number
WO 2017/103094 A3

(51) International Patent Classification:

A61K 31/30 (2006.01) *A61K 31/4166* (2006.01)
A61K 38/00 (2006.01) *A61P 1/16* (2006.01)
A61K 31/315 (2006.01)

(21) International Application Number:

PCT/EP2016/081407

(22) International Filing Date:

16 December 2016 (16.12.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

15201070.8 18 December 2015 (18.12.2015) EP
92979 19 February 2016 (19.02.2016) LU

(71) Applicants: **HELMHOLTZ ZENTRUM MÜNCHEN - DEUTSCHES FORSCHUNGSZENTRUM FÜR GESUNDHEIT UND UMWELT (GMBH)** [DE/DE]; Ingolstädter Landstraße 1, 85764 Neuherberg (DE). **THE REGENTS OF THE UNIVERSITY OF MICHIGAN** [US/US]; Office of Technology Transfer, 1600 Huron Parkway, 2nd Floor, Ann Arbor, Michigan 48109-2590 (US). **IOWA STATE UNIVERSITY RESEARCH FOUNDATION, INC.** [US/US]; 1805 Collaboration Place, Suite 2100, Ames, Iowa 50010 (US).

(72) Inventors: **ZISCHKA, Hans**; Pestalozzistraße 56, 80469 Munich (DE). **LICHTMANNEGGER, Josef**; Kreuzbergstraße 3, 85467 Neuching (DE). **DISPIRITO, Alan, Angelo**; 832 Ridgewood Ave, Ames, Iowa 50010 (US). **SEMRAU, Jeremy, David**; c/o University of Michigan, Civil and Environmental Engineering, An Arbor, Michigan 48109-2125 (US).

(74) Agents: **WEINZIERL, Gerhard** et al.; Schiweck Weinzierl Koch European Patent Attorneys, Landsberger Strasse 98, 80339 Munich (DE).

(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, 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:

27 July 2017

(54) Title: MEANS AND METHODS FOR TREATING COPPER-RELATED DISEASES

(57) Abstract: The present invention relates to the field of (bio-)medicine, and more particularly to the treatment of copper-related diseases. Novel means and methods for depleting (excess) copper from organs and/or the circulation are provided. Agents with a high copper binding affinity and stabilized forms thereof are provided, as well as a novel treatment regimen. The means and methods of the present invention are particularly useful for treatment of Wilson Disease, but also for treatment of other conditions.



WO 2017/103094 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081407

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/30 A61K38/00 A61K31/315 A61K31/4166 A61P1/16 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, WPI Data, BIOSIS, EMBASE								
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>X</td> <td> KARL H SUMMER ET AL: "The biogenic methanobactin is an effective chelator for copper in a rat model for Wilson disease", JOURNAL OF TRACE ELEMENTS IN MEDICINE AND BIOLOGY, FISCHER, NEW YORK, NY, US, vol. 25, no. 1, 8 December 2010 (2010-12-08), pages 36-41, XP028165079, ISSN: 0946-672X, DOI: 10.1016/J.JTEMB.2010.12.002 [retrieved on 2010-12-13] page 37, column 1, last paragraph figure 4 ----- -/-- </td> <td>1-20,30,31</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	KARL H SUMMER ET AL: "The biogenic methanobactin is an effective chelator for copper in a rat model for Wilson disease", JOURNAL OF TRACE ELEMENTS IN MEDICINE AND BIOLOGY, FISCHER, NEW YORK, NY, US, vol. 25, no. 1, 8 December 2010 (2010-12-08), pages 36-41, XP028165079, ISSN: 0946-672X, DOI: 10.1016/J.JTEMB.2010.12.002 [retrieved on 2010-12-13] page 37, column 1, last paragraph figure 4 ----- -/--	1-20,30,31
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.						
X	KARL H SUMMER ET AL: "The biogenic methanobactin is an effective chelator for copper in a rat model for Wilson disease", JOURNAL OF TRACE ELEMENTS IN MEDICINE AND BIOLOGY, FISCHER, NEW YORK, NY, US, vol. 25, no. 1, 8 December 2010 (2010-12-08), pages 36-41, XP028165079, ISSN: 0946-672X, DOI: 10.1016/J.JTEMB.2010.12.002 [retrieved on 2010-12-13] page 37, column 1, last paragraph figure 4 ----- -/--	1-20,30,31						
☒ 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						
1 June 2017		12/06/2017						
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 Büttner, Ulf						

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/081407

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GRACE E. KENNEY ET AL: "Chemistry and Biology of the Copper Chelator Methanobactin", ACS CHEMICAL BIOLOGY, vol. 7, no. 2, 17 February 2012 (2012-02-17), pages 260-268, XP055307727, US ISSN: 1554-8929, DOI: 10.1021/cb2003913 page 265, column 1, paragraph 1 -----	1-20,30, 31
A	WO 2004/056849 A2 (UNIV KANSAS [US]; UNIV IOWA STATE RES FOUND INC [US]; DISPIRITO ALAN A) 8 July 2004 (2004-07-08) examples 3,4 example 2 -----	1-31
A	M.-L. PESCH ET AL: "Competitive ligand exchange between Cu-humic acid complexes and methanobactin", GEOBIOLOGY, vol. 11, no. 1, 22 January 2013 (2013-01-22), pages 44-54, XP055307717, ISSN: 1472-4677, DOI: 10.1111/gbi.12010 table 1 -----	1-20,30, 31
A	MARIE-LAURE PESCH ET AL: "Copper complexation of methanobactin isolated from Methylosinus trichosporium OB3b: pH-dependent speciation and modeling", JOURNAL OF INORGANIC BIOCHEMISTRY, vol. 116, 1 November 2012 (2012-11-01), pages 55-62, XP055307730, US ISSN: 0162-0134, DOI: 10.1016/j.jinorgbio.2012.07.008 page 59, column 1 -----	1-20,30, 31
X	US 8 735 538 B1 (DISPIRITO ALAN ANGELO [US] ET AL) 27 May 2014 (2014-05-27) table I -----	21-23,29
Y		24-28, 30,31
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/081407

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHOI D W ET AL: "Spectral and thermodynamic properties of Ag(I), Au(III), Cd(II), Co(II), Fe(III), Hg(II), Mn(II), Ni(II), Pb(II), U(IV), and Zn(II) binding by methanobactin from Methylosinus trichosporium OB3b", JOURNAL OF INORGANIC BIOCHEMISTRY, ELSEVIER INC, US, vol. 100, no. 12, 1 December 2006 (2006-12-01), pages 2150-2161, XP027900346, ISSN: 0162-0134 [retrieved on 2006-12-01]	21-23,29
Y	table 4	24-28, 30,31
Y	----- MICHAEL L. SCHILSKY: "Treatment of Wilson's disease: What are the relative roles of penicillamine, trientine, and zinc supplementation?", CURRENT GASTROENTEROLOGY REPORTS, vol. 3, no. 1, 1 February 2001 (2001-02-01), pages 54-59, XP055374650, US ISSN: 1522-8037, DOI: 10.1007/s11894-001-0041-4 page 56 - page 57 -----	24-28, 30,31

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/081407

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.:

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-20, 30, 31

A copper binding methanobactin for use in the treatment of Wilson Disease wherein said treatment comprises at least one treatment cycle of a first phase of methanobactin administration followed by a second phase of non-treatment wherein the second phase exceeds the first phase.

2. claims: 21-29

A pharmaceutical composition comprising a stabilized methanobactin wherein said methanobactin complexes Zn and/or said pharmaceutical composition is provided at a pH equal or above 9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2016/081407

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004056849	A2	08-07-2004	AU 2003301104 A1 14-07-2004
			US 2004171519 A1 02-09-2004
			WO 2004056849 A2 08-07-2004

US 8735538	B1	27-05-2014	US 7932052 B1 26-04-2011
			US 8735538 B1 27-05-2014
