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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2023 (28.09.2023)

WIPO | PCT

(10) International Publication Number
WO 2023/183287 A3

(51) International Patent Classification:
C07D 233/64 (2006.01) *C07F 3/06* (2006.01)
A61K 31/4172 (2006.01) *C08G 83/00* (2006.01)
A61K 47/54 (2017.01)

(21) International Application Number:
PCT/US2023/015745

(22) International Filing Date:
21 March 2023 (21.03.2023)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/322,017 21 March 2022 (21.03.2022) US

(71) Applicant: **THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL** [US/US]; 109 Church Street, Chapel Hill, NC 27516 (US).

(72) Inventors: **AINSLIE, Kristy**; C/o Unc-eshelman Sch. Of Pharmacy-div. Of Mol., Pharma., 610 Brookgreen Drive, Chapel Hill, NC 27516-4465 (US). **BACHELDER, Eric**; C/o Unc-eshelman Sch. Of Pharmacy-div. Of Mol., Pharma., 610 Brookgreen Drive, Chapel Hill, NC 27516-4465 (US). **BATTY, Cole**; C/o Unc-eshelman Sch. Of Pharmacy-div. Of Mol., Pharma., 610 Brookgreen Drive, Chapel Hill, NC 27516-4465 (US). **LIFSHITS, Liubov**; C/o Unc-eshelman Sch. Of Pharmacy-div. Of Mol., Pharma., 610 Brookgreen Drive, Chapel Hill, NC 27516-4465 (US). **ROQUE, John, Andrew**; C/o Unc-eshelman Sch. Of Pharmacy-div. Of Mol., Pharma., 610 Brookgreen Drive, Chapel Hill, NC 27516-4465 (US).

(74) Agent: **WIMBISH, J., Clinton**; Nexsen Pruet, PLLC, 227 West Trade Street, Suite 1550, Charlotte, NC 28202 (US).

(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, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, 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, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, 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, ME, 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))*

(88) Date of publication of the international search report:
21 December 2023 (21.12.2023)

(54) Title: COMPOSITE BIOACTIVE COMPOSITIONS AND APPLICATIONS THEREOF

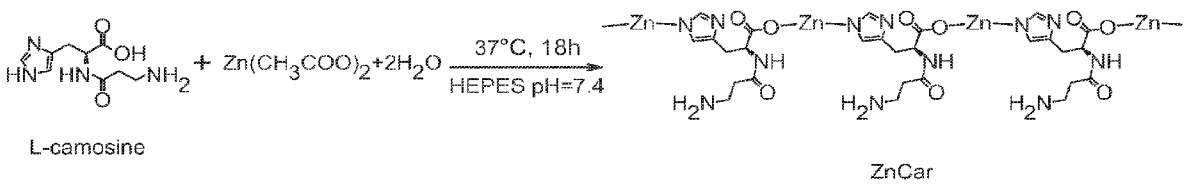

FIG. 1C

(57) Abstract: In one aspect, composite compositions are described herein for delivery of various bioactive compositions. In some embodiments, a composite composition comprises a metal- organic coordination polymer matrix, and one or more bioactive compositions carried by the metal-organic coordination polymer matrix, wherein the metal-organic coordination polymer matrix comprises polymeric chains including a repeating unit of formula I.

WO 2023/183287 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/15745

A. CLASSIFICATION OF SUBJECT MATTER

IPC - INV. C07D 233/64; A61K 31/4172; A61K 47/54; C07F 3/06; C08G 83/00 (2023.01)
ADD.

CPC - INV. C08G 83/001; A61K 31/4172; A61K 47/547; C07D 233/64; C07F 3/06
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)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	(HUANG, W et al.) His6-metal assemblies: a novel and promising drug delivery system. 25 January 2019, [retrieved on 2023-05-23]. Retrieved from the Internet URL: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3320742; https://papers.ssrn.com/sol3/Delivery.cfm/ACTA_MATERIALIA-1548180783400.pdf?abstractid=3320742&mirid=1, page 1-15; abstract; page 1, first column, first paragraph; page 2, first column, second paragraph; page 3, second column, second paragraph; page 4, first column, third paragraph; page 12, figures 1-3; page 15, table 1	1, 7-25, 38, 39/1, 39/7-25, 39/38, 40/39/1, 40/39/7-25, 40/39/38, 41, 44-49 --- 2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
Y --- A	(UNNO, H et al.) Structural Basis for Substrate Recognition and Hydrolysis by Mouse Carnosinase CN2. The Journal of Biological Chemistry, Vol. 283, No. 40, 3 October 2008, doi: 10.1074/jbc.M801657200, pages 27289-27299; page 27290, second column, first paragraph; page 27296, figure 7C	1, 7-25, 38, 39/1, 39/7-25, 39/38, 40/39/1, 40/39/7-25, 40/39/38, 41, 44-49 --- 2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26 and 42-43
Y	WO 2019/145475 A2 (ACM BIOLABS PTE LTD) 01 August 2019; paragraphs [009], [0044], [0048], [0050], [0093], [00103], [00155], [00158]; claim 70	8-9, 23, 39/8-9, 39/23, 40/39/8-9, 40/39/23, 44-47
Y	US 8,791,239 B2 (SHI, XW et al.) 29 July 2014; abstract; figures 1-2; column 9, lines 40-45; claim 1	14, 39/14, 40/39/14

☒ 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
"D" document cited by the applicant in the international application
"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
26 July 2023 (26.07.2023)	NOV 06 2023
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/15745

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2021/081043 A1 (THE JOHNS HOPKINS UNIVERSITY) 29 April 2021; abstract; page 35, lines 15-20; page 51, lines 20-30; page 55, lines 15-25	16-18, 39/16-18, 40/39/16-18
Y	WO 2014/142653 A1 (CRISTAL DELIVERY B.V.) 18 September 2014; abstract; page 9, lines 25-30; page 10, lines 20-25; page 24, lines 20-25; page 34, lines 1-5; page 39, lines 5-10	16, 19-20, 39/16, 39/19-20, 40/39/16, 40/39/19-20
Y	WO 2020/223395 A1 (THE RESEARCH FOUNDATION FOR THE STATE UNIVERSITY OF NEW YORK) 05 November 2020; paragraphs [0009], [0049], [0096], [0128]; figure 1	38, 39/38, 40/39/38
Y	(PARK, IK et al.) Abstract #4465: Development of mannan-coated iron oxidenanoparticles specifically interacting with mannose receptors on macrophages for detection of metastatic breastcancer in lymph node. Cancer Research, Vol. 69, No. 9, Supplement, publication 4465, 2009, [retrieved on 2023-05-23]. Retrieved from the Internet URL: https://aacrjournals.org/cancerres/article/69/9_Supplement/4465/555389; abstract	39/1, 39/7-25, 39/38, 40/39/1, 40/39/7-25, 40/39/38
A	(MATSUKURA, T et al.) Applicability of Zinc Complex of L-Carnosine for Medical Use. Biochemistry (Moscow), Vol. 65, No. 7, July 2000, pages 817-823; page 819, figure 1; page 819, second column, first paragraph	2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
A	WO 2016/057910 A1 (DI ROCCO, RJ et al.) 14 April 2016; paragraph [0004]	2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
A	US 2015/0328314 A1 (THE CURATORS OF THE UNIVERSITY OF MISSOURI) 19 November 2015; figure 13; paragraph [0175]	2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
A	(XU, Y et al.) Histidine polypeptide-hybridized nanoscale metal–organic framework to sense drug loading/release. Materials and Design, Vol. 205, 2021, publication 109741, pages 2-9; abstract; page 3, figure 1	2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
A	JP 4936737 B2 (TOKUYAMA CORP) 23 May 2012, translation; paragraph [0003], original	2-6, 26, 39/2-6, 39/26, 40/39/2-6, 40/39/26, 42-43
P,X	(LEVI, ME et al.) Metal-Organic Coordination Polymer for Delivery of a Subunit Broadly Acting Influenza Vaccine. ACS Applied Materials and Interfaces, Vol. 14, No. 25, 29 June 2022, doi: 10.1021/acsami.2c04671, pages 28548-28558; entire publication	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US23/15745

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:
-***-Please See Supplemental Page-***-

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.:
Group I+, claims 1-49 are directed toward a composite composition comprising: a metal-organic coordination polymer matrix zinc-carnosine coordination polymer (first exemplary coordination polymer), and methods associated therewith.

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.

-***-Continued From Box No. III: 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 I+, claims 1-49 are directed toward a composite composition comprising: a metal-organic coordination polymer matrix zinc-carnosine coordination polymer (first exemplary coordination polymer), and methods associated therewith.

The compounds and methods of Claims 1-26, 38-49 are believed to encompass the first named invention of Groups I+ and are the claims that will be searched to the extent that they encompass a composite composition comprising: a metal-organic coordination polymer matrix zinc-carnosine coordination polymer (first exemplary coordination polymer), and methods associated therewith. This first named invention of Group I+ has been selected to encompass the first species of the genus found in claims 1-2 and 26 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines, where claim 26 provides the first complete example of the metal-organic coordination polymer matrix.

Applicant is invited to elect additional compounds, with specified substituents for each Rx, and where available as an option within at least one searchable claim, to be searched. Additional compound(s) will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected compound(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a composite composition comprising: a metal-organic coordination polymer matrix, wherein the repeating unit comprises zinc and His-Asp-OH (second exemplary coordination polymer), and methods associated therewith.

Groups I+ share the technical features including a composite composition comprising: a metal-organic coordination polymer matrix; and one or more bioactive compositions carried by the metal-organic coordination polymer matrix, wherein the metal-organic coordination polymer matrix comprises polymeric chains including a repeating unit of formula I where M is a transition metal, L is a linker including R, wherein R comprises a moiety for coordinating with the transition metal, and a method of treating a patient comprising: providing a composite composition including a metal-organic coordination polymer matrix, and one or more bioactive compositions carried by the metal-organic coordination polymer matrix, wherein the metal-organic coordination polymer matrix comprised polymeric chains including a repeating unit of formula I: where M is a transition metal, and L is a linker including R, wherein R comprises a moiety for coordinating with the transition metal; and administering the composite composition to the patient.

However, these shared technical features are previously disclosed by the publication entitled "His6-metal assemblies: a novel and promising drug delivery system" by Huang, et al. (hereinafter "Huang") in view of the publication entitled "Structural Basis for Substrate Recognition and Hydrolysis by Mouse Carnosinase CN2" by Unno, et al. (hereinafter "Unno").

Huang discloses a composite composition (particles of His6-metal assemblies HmA having high loading capacity of encapsulation of loadable drugs, were produced by coordinative interactions between histidine and metal ions; abstract; page 12, figures 1-2) comprising: a metal-organic coordination polymer matrix (HmA particles having coordinative interactions between histidine and metal ions, were generated by adding zinc ions into a hexahistidine His6 solution; abstract; page 2, first column, second paragraph; page 12, figures 1-2); and one or more bioactive compositions carried by the metal-organic coordination polymer matrix (a common drug Dextromethorphan DXM was encapsulated in Bis-Tris buffer solutions, i.e., as the composition, into the HmA particles; abstract; page 3, second column, second paragraph; page 4, first column, third paragraph; page 15, table 1), wherein the metal-organic coordination polymer matrix comprises polymeric chains (particles of His6-metal assemblies HmA were produced by coordinative interactions between histidine and metal ions, as shown in figures 1-2, zinc ions link hexa histidine His6 into a three-dimensional polymeric matrix; abstract; page 12, figures 1-2) including a repeating unit (multiple or repeating interactions of Zn ions with N1 nitrogen atom of the imidazole rings of the histidine moiety produces a three-dimensional polymeric network, as shown in figures 1-2; abstract; page 12, figures 1-2) of formula similar to the formula I (the second structure in second column in figure 2 shows interaction of Zn ion with N1 nitrogen atom of the imidazole ring of the histidine moiety; abstract; page 12, figures 1-2): where M is a transition metal (the HmA particles comprise zinc, where zinc is the transition metal, as disclosed in claim 25 of the instant application; abstract; page 12, figures 1-2), L is a linker including R, wherein R comprises a moiety for coordinating with the transition metal (in HmA particles, the hexa histidine His6 comprises additional imidazole rings that participate in coordination with other zinc ions; abstract; page 12, figures 1-2), a method of treating a patient (encapsulation of DXM allows the system to be used for the co-encapsulation of multiple drugs simultaneously for the treatment of cancers; page 3, second column, second paragraph) comprising: providing a composite composition (particles of His6-metal assemblies HmA having high loading capacity of encapsulation of loadable drugs, were produced by coordinative interactions between histidine and metal ions; abstract; page 12, figures 1-2) including a metal-organic coordination polymer matrix (HmA particles having coordinative interactions between histidine and metal ions, were generated by adding zinc ions into a hexahistidine His6 solution; abstract; page 2, first column, second paragraph; page 12, figures 1-2), and one or more bioactive compositions carried by the metal-organic coordination polymer matrix (a common drug Dextromethorphan DXM was encapsulated in Bis-Tris buffer solutions, i.e., as the composition, into the HmA particles; abstract; page 3, second column, second paragraph; page 4, first column, third paragraph; page 15, table 1), wherein the metal-organic coordination polymer matrix comprised polymeric chains (particles of His6-metal assemblies HmA were produced by coordinative interactions between histidine and metal ions, as shown in figures 1-2, zinc ions link hexa histidine His6 into a three-dimensional polymeric matrix; abstract; page 12, figures 1-2) including a repeating unit (multiple or repeating interactions of Zn ions with N1 nitrogen atom of the imidazole rings of the histidine moiety produces a three-dimensional polymeric network, as shown in figures 1-2; abstract; page 12, figures 1-2) of formula similar to the formula I (the second structure in second column in figure 2 shows interaction of Zn ion with N1 nitrogen atom of the imidazole ring of the histidine moiety; abstract; page 12, figures 1-2): where M is a transition metal (the HmA particles comprise zinc, where zinc is the transition metal, as disclosed in claim 25 of the instant application; abstract; page 12, figures 1-2), and L is a linker including R, wherein R comprises a moiety for coordinating with the transition metal (in HmA particles, the hexa histidine His6 comprises additional imidazole rings that participate in coordination with other zinc ions; abstract; page 12, figures 1-2); and administering the composite composition to the patient (Nanomedicine is revolutionizing traditional drug administration, encapsulation of DXM allows the system to be used for the co-encapsulation of multiple drugs simultaneously for the treatment of cancers; page 1, first column, first paragraph; page 3, second column, second paragraph). Huang does not disclose a formula in which the N3 nitrogen atom of the imidazole ring is not linked to a hydrogen, or unprotonated. However, Unno discloses the formula in which the N3 nitrogen atom of the

-***-Continued Within the Next Supplemental Box-***-

-***-Continued from previous Supplemental Box-***-

imidazole ring is not linked to a hydrogen, or unprotonated (the N3 nitrogen atom of the imidazole ring is not linked to a hydrogen, or unprotonated, in in the complex of zinc with histidine moieties in figure 7C; page 27296, figure 7C). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the composition, as previously disclosed by Huang, in order to have provided for the formula in which the N3 nitrogen atom of the imidazole ring is not linked to a hydrogen, or unprotonated, as previously disclosed by Unno (Unno; page 27296, figure 7C), for providing an alternative hypothetical representation of the imidazole moiety in the coordination complex of zinc with histidine moieties (Huang; abstract; page 12, figures 1-2) (Unno; page 27296, figure 7C). Further, provided that Huang and Unno both disclose the complex comprising zinc and histidine moieties (Huang; abstract; page 12, figures 1-2) (Unno; page 27296, figure 7C), where the complex is generated at neutral pH that does not support protonation of the heterocyclic nitrogen atoms (Huang; abstract; page 12, figures 1-2), the modification to Huang's composition, of providing for the formula in which the N3 nitrogen atom of the imidazole ring is not linked to a hydrogen, or unprotonated, would provide the benefit of for providing an alternative hypothetical representation of the imidazole moiety in the coordination complex of zinc with histidine moieties (Huang; abstract; page 12, figures 1-2) (Unno; page 27296, figure 7C).

Since none of the special technical features of the Group I+ is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Huang and Unno references, unity of invention is lacking.