



(51) International Patent Classification:

A61K 49/10 (2006.01) C07D 257/02 (2006.01)

(21) International Application Number:

PCT/US2019/029102

(22) International Filing Date:

25 April 2019 (25.04.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/663,671 27 April 2018 (27.04.2018) US

(71) Applicant: **UNIVERSITY OF IOWA RESEARCH FOUNDATION** [US/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US).

(72) Inventors; and

(71) Applicants: **SCHULTZ, Michael, K.** [US/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US). **PIGGE, Christopher** [US/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US). **LI, Mengshi** [CN/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US). **GABR, Moustafa** [EG/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US). **SAGAS-**

TUME, Edwin [US/US]; 2660 University Capitol Center, Iowa City, Iowa 52242 (US).

(74) Agent: **VIKSNINS, Ann, S.** et al.; Viksnins Harris Padys Malen LLP, 7851 Metro Parkway, Suite 325, Bloomington, Minnesota 55425 (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, 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,

(54) Title: COMPOSITIONS FOR CHELATING METALS AT LOW TEMPERATURES

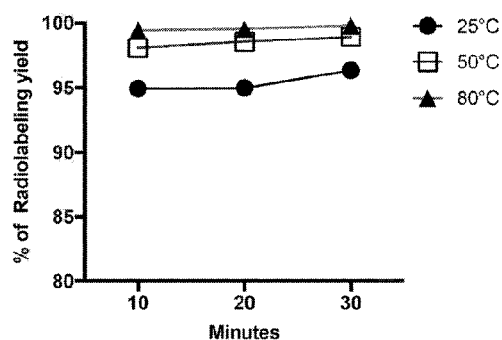
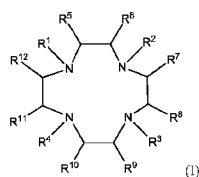


Figure 20



(57) Abstract: A method of performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I): or a salt thereof wherein: each of R^1 - R^4 is independently selected from the group consisting of CH_2COOR^a and $\text{CH}_2\text{C}(=\text{O})\text{NHR}^a$; each of R^5 - R^{12} is independently selected from the group consisting of H and -L-X; each R^a is independently selected from the group consisting of H and -L-X; each L is independently selected from the group consisting of absent and a linking group; and each X is a biological agent; and wherein the contacting occurs at a temperature below about 40°C to form a chelated composition.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

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

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

23 July 2020 (23.07.2020)

(15) Information about Correction:

see Notice of 06 February 2020 (06.02.2020)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/29102

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 49/10; C07D 257/02 (2019.01)

CPC - A61K 49/105; A61K 49/106; A61K 49/108; C07D 257/02

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 data base consulted during the international search (name of data base 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	US20170266304A1 (GE HEALTHCARE AS) 21 September 2017 (21.09.2017) entire document especially ; para [0040]; [0123]; Scheme 1	1 ----- 2-7 and 26-29
Y -- A	WO 2017/165473 A1 (The Johns Hopkins University) 28 September 2017 (28.09.2017) entire document especially page 5, In 19 to page 6, In 9	1 ----- 2-7 and 26-29
A	US 2008/0193384 A1 (Willard et al.) 14 August 2008 (14.08.2008) entire document especially abstract; para [0019]; figure 1, 4.	26-29
A	Corbin et al., "Screening of ligands for redox-active europium using magnetic resonance imaging", Bioorganic & Medicinal Chemistry 26 (2018) 5274-5279	1-7 and 26-29
A	US 5,435,990 A (Cheng et al.) 25 July 1995 (25.07.1995) entire document	1-7 and 26-29
A	US 9,579,404 B2 (New York University) 28 February 2017 (28.02.2017) entire document	1-7 and 26-29

☐ 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

31 December 2019

Date of mailing of the international search report

17 JAN 2020

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Lee Young

Telephone No. PCT Helpdesk: 571-272-4300

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 19/29102

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.: 8-25 and 30-64
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 box ---

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.

Box III: lack of unity

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 searched, the appropriate additional search fees must be paid.

Group I: Claims 1-7, directed to a method of performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I).

Group II: Claims 26-29, directed to a method of diagnosing a disease in a patient in need thereof, comprising: performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I) and administering the chelated composition to the patient within two hours of the chelating reaction.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group II requires a method of diagnosing a disease in a patient in need thereof, comprising: performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I) and administering the chelated composition to the patient within two hours of the chelating reaction, not required by group I.

Common Technical Features:

Groups I and II share the technical feature of a performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I).

However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is being anticipated by the document entitled Screening of ligands for redox-active europium using magnetic resonance imaging to Corbin et al. (hereinafter 'Corbin'). Corbin teaches the method of performing a chelating reaction comprising contacting a divalent metal with a compound of Formula (I) wherein each of R1-R4 is independently selected from the group consisting of CH₂COOR_a, R_a=H; each of R5-R12 is independently selected from the group consisting of H (page 5277, figure 2, formula 7) wherein the contacting occurs at a temperature below about 40°C to form a chelated composition (page 5276, col 2, results and discussion: "...mixing of the metal salt and ligand solutions...Corbin conducted the reaction at room temperature as there is no mention of heating)

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-II lack unity under PCT Rule 13.

Note:

Claims 8-25 and 30-64 determined unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).