



(51) International Patent Classification:

A61K 51/00 (2006.01) *A61K 38/04* (2006.01)
A61M 36/14 (2006.01)

(21) International Application Number:

PCT/US2012/037678

(22) International Filing Date:

12 May 2012 (12.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/485,528 12 May 2011 (12.05.2011) 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, 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, KM, 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, 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, ML, MR, NE, SN, TD, TG).

Published:

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

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

8 May 2014

(54) Title: METALLODRUGS HAVING IMPROVED PHARMACOLOGICAL PROPERTIES, AND METHODS OF MANUFACTURE AND USE THEREOF

(57) Abstract: It is an object of the present invention to provide improved pharmacological properties to molecules which bind to a target with low affinity (hereinafter referred to as a "ligand moiety") through linkage of such molecules to a metal binding moiety, thereby generating a combination molecule commonly referred to as a "metallodrug" or "metallotherapeutic." The metal binding domain of metallodrugs typically catalyzes oxido-reductase chemistry or acts as a Lewis-Acid catalyst, resulting in modification of proteins and nucleic acids that are in close proximity due to binding of the ligand moiety to its target.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/37678

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 51/00; A61M 36/14; A61K 38/04 (2012.01)

USPC - 424/1.61, 424/1.65

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)

IPC(8) - A61K 51/00; A61M 36/14; A61K 38/04 (2012.01)

USPC - 424/1.61, 424/1.65

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

USPC - 530/330, 540/474

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase; PubMed (MEDLINE)

metal, catalytic, inactivation, inhibition, coordination, metallodrug, metallotherapeutic, metallopharmaceutic, binding, affinity, covalent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2006/0019942 A1 (MEGGERS et al.) 26 January 2006 (26.01.2006) para [0009], [0010], [0011], [0047], [0061], [0062], [0067], [0066], [0069], [0104], [0137]; Fig 1, 3	1, 12-15, 19-20 ----- 2-3, 7-11, 16-18, 21
Y	DOUGAN et al., Catalytic organometallic anticancer complexes. Proc Natl Acad Sci U S A. (19 August 2008, published online 07 August 2008) vol 105, no 33, pp 11628-33; abstract; pg 11628, col 1, para 1; pg 11629, col 2, para 3; pg 11632, col 1, para 3	2, 9
Y	THAMAPIPOL et al. Chiral ruthenium Lewis acid catalyzed intramolecular Diels-Alder reactions. Org Lett. (17 December 2010, published online 17 November 2010) vol 12, no 24, pp 5604-7. pg 5604, col 1, para 1-2	3
Y	US 2008/0188422 A1 (COWAN et al.) 07 August 2008 (07.08.2009) para [0045], [0046], [0056], [0069]	7-8, 16-18
Y	US 7,635,762 B2 (COOK et al.) 22 December 2009 (22.12.2009) col 3, ln 53-63; col 13, ln 13-18; col 52, ln 24-32	10-11
Y	ANAND et al. Toward the development of a potent and selective organoruthenium mammalian sterile 20 kinase inhibitor. J Med Chem. (March 2009) vol 52, no 6. pp 1602-11; Fig 5D	21

☒ Further documents are listed in the continuation of Box C.

* 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

18 October 2012 (18.10.2012)

Date of mailing of the international search report

05 NOV 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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Facsimile No. 571-273-3201

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PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0213172 A1 (Babich et al.) 04 September 2008 (04.09.2008) whole doc.	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/37678

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.: 4-6, 25, 27-29 and 45-47
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 extra sheet for continuation -

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.: 1-3, 7-21

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 12/37678

Continuation of:

Box No III. Observations where unity of invention is lacking

Group I: claims 1-3, 7-21, drawn to a composition for catalytically inactivating a biochemical target of interest, comprising: a ligand moiety which binds to the biochemical target with an affinity of between about 10 M^{-1} and about $5 \times 10^8\text{ M}^{-1}$, a metal binding moiety, wherein the ligand moiety and the metal binding moiety are covalently linked.

Group II: claims 22-24, 26, 30-44, drawn to a method of improving the efficacy of a current or candidate therapeutic molecule which is a ligand to a biochemical target, comprising: covalently conjugating said current or candidate therapeutic molecule and which lacks a metal binding domain, to a metal binding moiety.

Group III: claim 48, drawn to a method of sterilization by inactivating a biochemical target, comprising: administering to a subject in need thereof a composition according to the present invention under conditions wherein the composition binds to, and is active as a Lewis acid catalyst proximate to the biochemical target, wherein the concentration of reactive species generated conformationally and/or functionally alters the biochemical target to a therapeutic effect.

The inventions listed as Groups I through III 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:

The inventions of Groups I-II do not include the inventive concept of a method of sterilization by inactivating a biochemical target, as required by Group III.

The inventions of Group II-III do not include the inventive concept of a ligand moiety which binds to the biochemical target with an affinity of between about 10 M^{-1} and about $5 \times 10^8\text{ M}^{-1}$, as required by Group I.

The inventions of Groups I-III share the technical feature of a method of inactivating a biochemical target of interest, comprising: a ligand moiety which binds to the biochemical target, a metal binding moiety, wherein the ligand moiety and the metal binding moiety are covalently linked. However, this shared technical feature does not represent a contribution over prior art as being anticipated by US 2008/0213172 A1 to Babich et al. (hereinafter 'Babich'). Babich discloses a method of inactivating a biochemical target of interest (para [0009], lisinopril is an inhibitor of dipeptidyl carboxypeptidase, ACE, para [0011], radiotherapeutic moieties as a coupling partner for a peptidase-binding moiety), comprising: a ligand moiety which binds to the biochemical target (para [0009], lisinopril), a metal binding moiety (para [0009]), wherein the ligand moiety and the metal binding moiety are covalently linked (Figs. 6-7). As said composition was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Groups I through III therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.