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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 December 2014 (04.12.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/194280 A3

(51) International Patent Classification:
A61K 31/27 (2006.01)

(21) International Application Number:
PCT/US2014/040368

(22) International Filing Date:
30 May 2014 (30.05.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/828,749 30 May 2013 (30.05.2013) US
61/937,394 7 February 2014 (07.02.2014) US

(71) Applicant: **THE BOARD OF REGENTS OF THE NEVADA SYSTEM OF HIGHER EDUCATION on behalf of THE UNIVERSITY OF NEVADA, LAS VEGAS** [US/US]; 4505 S. Maryland Parkway, Las Vegas, NV 89154 (US).

(72) Inventor: **ZHANG, Hui**; 23 Tapadero Lane, Las Vegas, NV 89135 (US).

(74) Agents: **SHORTELL, D. Brian** et al.; Ballard Sphar LLP, 999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (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, 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, 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, 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, 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:
12 February 2015

(54) Title: NOVEL SUICIDAL LSD1 INHIBITORS TARGETING SOX2-EXPRESSING CANCER CELLS

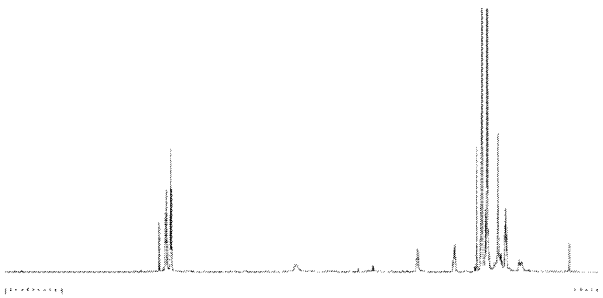


FIG. 1A

(57) Abstract: Disclosed are inhibitors of lysine-specific demethylase I (LSD1); synthetic methods for making the compounds; pharmaceutical compositions comprising the compounds; and methods of treating cancers characterized by the presence of Sox2 using the compounds and compositions Also disclosed are methods of treating cancers characterized by the presence of Sox2 using inhibitors of LSD 1 and/or histone deacetylation I (HDAC1). This abstract is intended as a scanning tool for purposes of searching in the particular art and is not intended to be limiting of the present invention.

WO 2014/194280 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/040368

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/27 (2014.01)
CPC - A61K 31/27 (2014.10)
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 31/27 (2014.01)
CPC - A61K 31/27 (2014.10) (keyword delimited)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/476, 491 (keyword delimited)

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

PatBase, Orbit, STN, PubChem, Google Scholar
Search terms used: cyclopropylamine, phenylcyclopropyl, cyclopropylphenyl, carbamic, carbamate, LSD1, lysine demethylase, cancer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	PubChem. Compound Summary for: CID 69685062. Create Date: 2012-12-01. [retrieved on 10 September 2014]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/69685062?from=summary>. entire document	1, 3, 4, 6, 8, 9 ---------- 13, 60-68
Y	WO 2013/057320 A1 (ORTEGA MUNOZ et al) 25 April 2013 (25.04.2013) entire document	13, 60-68
A	PubChem. Compound Summary for: CID 51034697. Create Date: 2011-04-18. [retrieved on 10 September 2014]. Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/compound/51034697?from=summary>. entire document	1, 3, 4, 6, 8, 9, 13, 60-68
A	WO 2012/135113 A2 (JOHNSON et al) 04 October 2012 (04.10.2012) entire document	1, 3, 4, 6, 8, 9, 13, 60-68

☐ 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	Date of mailing of the international search report
19 November 2014	10 DEC 2014
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. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/040368

<Continued from Box 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 need to be paid.

Group I+: claims 1-14 and 60-68 are drawn to a compound having a structure represented by the instant formula shown, pharmaceutical compositions thereof, and kits thereof.

Group II+: claims 15-46 are drawn to a method of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, and methods of treating cancer thereof.

Group III: claims 47-59 are drawn to a method of treating cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one HDAC1 inhibitor.

The first invention of Group I+ is restricted to a compound having a structure represented by the instant formula shown for claim 1, wherein L is a -O- moiety; wherein R1 is hydrogen; and wherein Ar1 is phenyl, and wherein Ar1 is substituted with 0 groups; and pharmaceutical compositions thereof, and kits thereof. It is believed that claims 1, 3, 4, 6, 8, 9, 13, and 60-68 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

The invention of Group II+ is restricted to a compound of the instant formula of claims 15 and 32, and methods of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, and methods of treating cancer thereof, wherein the instant formula of claims 15 and 32 is selected to be a specific compound such as wherein L is a -C(O)- moiety; wherein R1 is hydrogen; and wherein Ar1 is phenyl, and wherein Ar1 is substituted with 0 groups in an exemplary election.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound having a structure represented by the instant formula shown for claim 1, wherein L is a -(CR2aR2b)n- moiety; wherein n is 1; wherein each R2a and R2b is hydrogen; wherein R1 is hydrogen; and wherein Ar1 is phenyl, and wherein Ar1 is substituted with 0 groups; and pharmaceutical compositions thereof, and kits thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on 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.

The inventions listed in 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 special technical features of Group I+, compounds having a structure represented by the instant formula shown in claim 1, are not present in Groups II+ and III; the special technical features of Group II+, methods of inhibiting LSD1 (lysine-specific demethylase I), are not present in Groups I+ and III; and the special technical features of Group III, methods of treating cancer comprising administering an effective amount of at least one HDAC1 inhibitor, are not present in Groups I+ and II+.

The Groups I+ and II+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound variables L, R1, and Ar1.

The Groups I+ through III share the technical features of a compound having a structure represented by the instant formula shown in claim 1, or a pharmaceutically acceptable salt thereof; a compound having the structure selected from one of the formulas shown in claim 14; a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claims 1, or a pharmaceutically acceptable salt, solvate, or polymorph thereof; and a pharmaceutically acceptable carrier; a method of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, the method comprising the method comprising contacting the cell with an effective amount of at least one compound having a structure represented by the instant formula shown in claim 15; a method of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor; and a kit comprising at least one compound having a structure represented by the instant formula shown in claim 60, or a pharmaceutically acceptable salt thereof, and one or more of: a) at least one agent known to inhibit LSD1; b) at least one agent known to inhibit HDAC1; c) at least one anticancer therapeutic agent; d) instructions for detecting a cancer; and e) instructions for treating a cancer. However, these shared technical features do not represent a contribution over the prior art.

Specifically, "Compound Summary for: CID 69685062" to PubChem teaches a compound having a structure represented by the instant formula shown in claim 1, wherein L is a -O- moiety; wherein R1 is hydrogen; and wherein Ar1 is phenyl, and wherein Ar1 is substituted with 0 groups; or a pharmaceutically acceptable salt thereof (see structure shown...IUPAC Name: [(1R,2S)-2-phenylcyclopropyl] carbamic acid...).

Additionally, "Compound Summary for: CID 51034697" to PubChem teaches a compound having the structure selected from one of the formulas shown in claim 14, which corresponds to the to the second shown compound on the right, comprising a benzyloxy group and a piperazine group (see structure shown...IUPAC Name: (1R,2S)-N-[2-(4-methylpiperazin-1-yl ethyl]-2-(4-phenyl methoxyphenyl) cyclopropan-1-amine...).

Further, WO 2012/135113 to Johnson et al. teach a pharmaceutical composition comprising a therapeutically effective amount of at least one compound comprising the core structure of claim 1, or a pharmaceutically acceptable salt, solvate, or polymorph thereof; and a pharmaceutically acceptable carrier (see Pg. 21 Lns. 1-6, ...a pharmaceutical composition (also referred to as pharmaceutical formulation) comprising a compound of Formula (I) or pharmaceutically acceptable salt, thereof and one or more excipients (also referred to as carriers and/or diluents in the pharmaceutical arts)...; Pg. 152, Lns. 10-24); a method of inhibiting LSD1 (lysine-specific demethylase I) in at least one cell, the method comprising the method comprising contacting the cell with an effective amount of at least one compound (Pgs. 186-187 Lns. 15-28 and 1-5) having a structure represented by the instant formula shown in claim 15, wherein L is a -(CR2aR2b)n- moiety; wherein n is 1; wherein each of R2a and R2b is hydrogen; wherein R1 is Cy1; wherein Cy1, when present, is C2-C5 heterocycloalkyl and wherein Cy1, when present, is substituted with 0 groups (Pg. 57 Lns. 4-20, Example 6, [(1R,2S)-2-Phenylcyclopropyll(4-piperidinylmethyl)amine...); a method of treating a cancer in a mammal, the method comprising administering to the mammal an effective amount of at least one LSD1 inhibitor (Pgs. 4-5 Lns. 23-24 and 1-6); and a kit comprising at least one compound having a structure represented by the instant formula shown in claim 60, wherein L is a -(CR2aR2b)n- moiety; wherein n is 1; wherein each of R2a and R2b is hydrogen; wherein R1 is Cy1; wherein Cy1, when present, is C2-C5 heterocycloalkyl and wherein Cy1, when present, is substituted with 0 groups (Pg. 24 Lns. 26-29, for use in therapy, a therapeutically effective amount of a compound of Formula (I) or salt thereof may be administered as the raw chemical, it is typically presented as the active ingredient of a pharmaceutical composition or formulation...; Pg. 57 Lns. 4-20, Example 6, [(1R,2S)-2-Phenylcyclopropyll(4-piperidinylmethyl)amine...; Pg. 21, Lns. 21-28) or a pharmaceutically acceptable salt thereof, and one or more of: a) at least one agent known to inhibit LSD1; b) at least one agent known to inhibit HDAC1; c) at least one anticancer therapeutic agent; d) instructions for detecting a cancer; and e) instructions for treating a cancer (Pg. 25 Lns. 14-19, When a compound of Formula (I) is administered for the treatment of cancer, the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of a LSD1 inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer...; Pg. 40 Lns. 4-10).

The inventions listed in Groups I+ through III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.

<End Box III: Observations where unity of invention is lacking>