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(88) Date of publication of the international search report:
5 November 2015

[Continued on next page]

(54) Title: NRF2 SMALL MOLECULE INHIBITORS FOR CANCER THERAPY

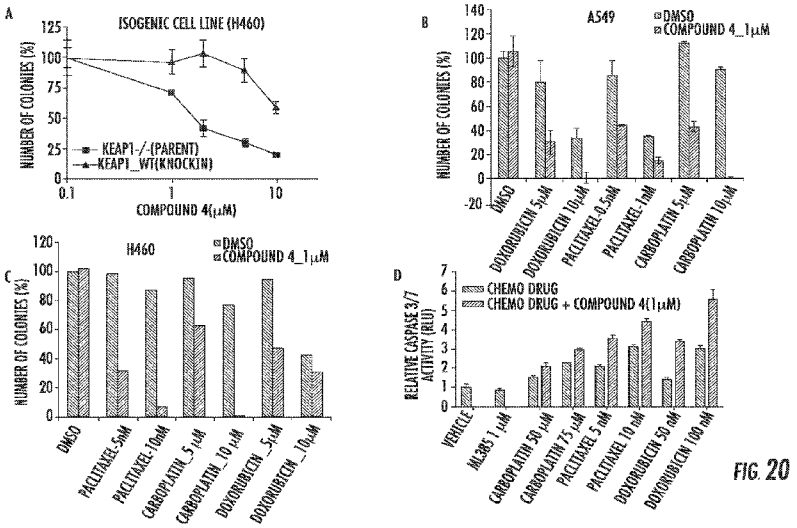


FIG. 20

(57) Abstract: Small molecule inhibitors of Nrf2 and methods of their use are provided for treating or preventing a disease, disorder or condition associated with an Nrf2- regulated pathway. The compound can be administered as a single agent or can be administered to enhance the efficacy of a chemotherapeutic drug and/or radiation therapy.

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(15) **Information about Correction**:

Previous Correction:
see Notice of 13 November 2014

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/030442

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 277/44 (2014.01)
USPC - 514/415
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 31/404; C07D 209/04, 277/44 (2014.01)
USPC - 514/371, 415; 548/190, 469

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/404; C07D 209/04, 277/44 (2014.09)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Patents, STN, Google Scholar, PubChem

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7,595,398 B2 (SCHMITZ et al) 29 September 2009 (29.09.2009) entire document	1
A	PubChem, Compound Summary for CID 3643359, Create Date: 2005-09-10. [retrieved on 18 July 2014]. Retrieved from the Internet. <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3643359> entire document	1
A	PubChem, Compound Summary for CID 44182149, Create Date: 2009-09-01. [retrieved on 18 July 2014]. Retrieved from the Internet. <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=44182149> entire document	1
A	PubChem, Compound Summary for CID 220406, Create Date: 2005-03-26. [retrieved on 21 July 2014]. Retrieved from the Internet. <URL: http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=220406> entire document	1
A	WO 2008/124000 A2 (ZHI et al) 16 October 2008 (16.10.2008) entire document	1
A	WO 2007/076055 A2 (HEMBROUGH et al) 05 July 2007 (05.07.2007) entire document	1

☐ 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
17 October 2014	13 NOV 2014

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/030442

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:

Claim 1 has been analyzed subject to the restriction that the claims read on the formula (1a) as described in the Lack of Unity of Invention (See Extra Sheet). The claim is restricted to a compound of formula (1a): wherein: m is 0; n is 0; each p is 0; R1a is H; R2a is a substituted or unsubstituted straight-chain alkyl; R3a is H; R6a is H; Y is -(C=O)-; and Z is R6a.

See Extra 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 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

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/US2014/030442

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 1-7 are drawn to compounds of formula (1a), (1b), and (1c); or an enantiomer, diastereomer, racemate or pharmaceutically acceptable salt, prodrug, or solvate thereof.

Group II+ claims 8-20 are drawn to compounds of formula (2a), (2b), (2c), or (3); or an enantiomer, diastereomer, racemate or pharmaceutically acceptable salt, prodrug, or solvate thereof.

Group III: claims 21-39 are drawn to methods for treating or preventing a disease, disorder or condition associated with an Nrf2-regulated pathway.

The first invention of Group I+ is restricted to a compound of formula (1a): wherein: m is 0; n is 0; each p is 0; R1a is H; R2a is a substituted or unsubstituted straight-chain alkyl; R3a is H; R6a is H; Y is -(C=O)-; and Z is R6a. It is believed that claim 1 reads 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 formula (2a), wherein formula (2a) is selected to be a specific compound such as wherein: m' is 0; n' is 0; each p is 0; R1b is H; and R2b is a substituted or unsubstituted straight-chain alkyl 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 of formula (1a): wherein: m is 1; n is 0; each p is 0; R1a is H; R2a is a substituted or unsubstituted straight-chain alkyl; R3a is H; R4a is H; R6a is H; Y is -(C=O)-; and Z is R6a. 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 of formula (1a), (1b), and (1c), are not present in Groups II+ and III; the special technical features of Group II+, compounds of formula (2a), (2b), (2c), or (3), are not present in Groups I+ and III; and the special technical features of Group III, methods for treating or preventing a disease, disorder or condition associated with an Nrf2-regulated pathway, are not present in Groups I+ and II+.

The Groups I+ formulae (1a), (1b), and (1c) do not share a significant structural element, requiring the selection of alternatives for the compound variables m, n, p, R1a, R2a, R3a, R4a, R5a, Y, and Z.

The Groups II+ formulae (2a), (2b), (2c), and (3) do not share a significant structural element, requiring the selection of alternatives for the compound variables m', n' p, R1b, R2b, R3b, R4b, R5b, R6b, R7b, R8b, R9b, and R10b; or n", A, B, R1c, R2c, and R3c.

The Groups I+ through III share the technical features of a compound having the core structure of of formula (1), formula (2), or formula (3); or an enantiomer, diastereomer, racemate or pharmaceutically acceptable salt, prodrug, or solvate thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, "Compound Summary for: CID 3643359" to PubChem teaches a compound of formula (1a), wherein: m is 0; n is.0; each p is 0; R1a is H; R2a is unsubstituted straight-chain alkyl; R3a is H; R6a is unsubstituted straight-chain alkyl; Y is -(C=O)-; and Z is -C(=O)-(CH2)p-R6a (see structure shown for CID 3643359...IUPAC Name: N-[4-(1-propanoyl-2,3-dihydroindol-5-yl)-1,3-thiazol-2-yl] propanamide...).

Additionally, "Compound Summary for: CID 44182149" to PubChem teaches a compound having the core structure of formula (2a), wherein: m' is 0; n' is 0; p is 1; R1b is H; and R2b is unsubstituted straight-chain alkyl (see structure shown for CID 44182149...IUPAC Name: 4-(3,4-dihydro-1H-isoquinolin-2-ylmethyl)-N-(4-methylsulfanylphenyl)benzamide...).

Further, "Compound Summary for: CID 220406" to PubChem teaches a compound of formula (3), wherein: each n" is 0; A is a ring selected as the shown phenyl ring; B is a ring selected as the shown furan ring; wherein the ring structure A and ring structure B are connected via an amide linkage represented by -NR1cC(=O)-; and R1c is H (see structure shown for 2-Furanilide...IUPAC Name: N-phenylfuran-2-carboxamide...).

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.