

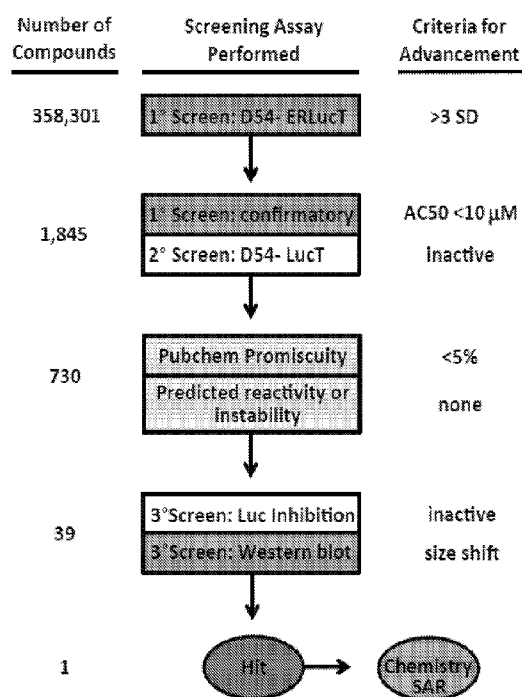


- (51) **International Patent Classification:**
C07C 311/20 (2006.01) *C07C 311/15* (2006.01)
A61K 31/166 (2006.01) *C07D 277/20* (2006.01)
A61K 31/18 (2006.01)
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- (71) **Applicants:** YALE UNIVERSITY [US/US]; Two Whitney Avenue, New Haven, Connecticut 06511 (US). THE UNIVERSITY OF KANSAS [US/US]; 245 Strong Hall, 1450 Jayhawk Boulevard, Lawrence, Kansas 66045 (US).
- (72) **Inventors:** CONTESSA, Joseph N.; 322 Willow Road, Guilford, Connecticut 06437 (US). GOLDEN, Jennifer E.; 777 Highland Avenue, Madison, Wisconsin 53705 (US). FLAHERTY, Daniel P.; 85 Chattan Drive, West Lafayette, Indiana 47906 (US).
- (74) **Agents:** DOYLE, Kathryn et al.; Saul Ewing LLP, 1500 Market Street, 38th Floor, Philadelphia, Pennsylvania 19102 (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, 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,

[Continued on next page]

(54) **Title:** INHIBITORS OF N-LINKED GLYCOSYLATION AND METHODS USING SAME

FIG. 1A



(57) **Abstract:** The present invention includes novel compounds and methods for preventing or treating diseases associated with N-linked glycosylation in a subject in need thereof. The methods comprise administering to the subject an effective amount of at least one compound of the invention.

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

Published:

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- *of inventorship (Rule 4.17(iv))*

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6 April 2017

INTERNATIONAL SEARCH REPORT

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<p>A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - C07C 311/20; A61K 31/166; A61K 31/18; C07C 311/15; C07D 277/20 (2016.01) CPC - C07C 311/20; A61K 31/166; A61K 31/18; C07C 311/15; C07D 277/20 (2016.11) According to International Patent Classification (IPC) or to both national classification and IPC</p>																	
<p>B. FIELDS SEARCHED</p> <p>Minimum documentation searched (classification system followed by classification symbols) IPC - A61K 31/166; A61K 31/18; C07C 311/15; C07C 311/20; C07D 277/20 CPC - A61K 31/166; A61K 31/18; C07C 311/15; C07C 311/20; C07D 277/20</p> <p>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/317; 514/319; 514/602; 546/205; 564/86; IPC - A61K 31/166; A61K 31/18; C07C 311/15; C07C 311/20; C07D 277/20; CPC - A61K 31/166; A61K 31/18; C07C 311/15; C07C 311/20; C07D 277/20 (keyword delimited)</p> <p>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) Orbit, Google Patents, Google, PubChem, SureChem, STN Search terms used: Inhibitors, N-Linked Glycosylation, sulfamoyl, benzamide, pyrrolidine, thiazole</p>																	
<p>C. DOCUMENTS CONSIDERED TO BE RELEVANT</p> <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>PUBCHEM: Substance Record for SID 111590126. 07 March 2011. [retrieved on 16.09.2016] Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/substance/111590126>. entire document</td> <td>1-4, 6, 12, 13</td> </tr> <tr> <td>A</td> <td>US 2006/0079557 A1 (DOLLE et al) 13 April 2006 (13.04.2006) entire document</td> <td>1-4, 6, 12, 13</td> </tr> <tr> <td>A</td> <td>US 2010/0016310 A1 (INGRAHAM) 21 January 2010 (21.01.2010) entire document</td> <td>1-4, 6, 12, 13</td> </tr> <tr> <td>A</td> <td>US 2006/0135773 A1 (SEMPLÉ et al) 22 June 2006 (22.06.2006) entire document</td> <td>1-4, 6, 12, 13</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	PUBCHEM: Substance Record for SID 111590126. 07 March 2011. [retrieved on 16.09.2016] Retrieved from the Internet. <URL: https://pubchem.ncbi.nlm.nih.gov/substance/111590126>. entire document	1-4, 6, 12, 13	A	US 2006/0079557 A1 (DOLLE et al) 13 April 2006 (13.04.2006) entire document	1-4, 6, 12, 13	A	US 2010/0016310 A1 (INGRAHAM) 21 January 2010 (21.01.2010) entire document	1-4, 6, 12, 13	A	US 2006/0135773 A1 (SEMPLÉ et al) 22 June 2006 (22.06.2006) entire document	1-4, 6, 12, 13
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<p><input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.</p>																	
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td style="vertical-align: top;"> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </td> <td style="vertical-align: top;"> <p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p> </td> </tr> </table>			<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"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</p> <p>"&" document member of the same patent family</p>													
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<p>Date of the actual completion of the international search</p> <p>29 November 2016</p>		<p>Date of mailing of the international search report</p> <p style="font-size: 24pt; text-align: center;">15 FEB 2017</p>															
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300</p>		<p>Authorized officer</p> <p style="text-align: center;">Blaine R. Copenheaver</p> <p>PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774</p>															

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2016/043664

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:

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.:
1-4, 6, 12, 13

- 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/US2016/043664

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-4, 6, 12, and 13 have been analyzed subject to the restriction that the claims read on a compound of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof, wherein R1 is the first shown structure; R2 is the first shown structure; R3 is the first shown structure; each occurrence of R4 is H; wherein R3 is attached para to the sulfoxide group; and pharmaceutical compositions thereof.

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 1-13 are drawn to compounds of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof and pharmaceutical compositions thereof.

Group II: claims 14-32 are drawn to methods of inhibiting or disrupting N-linked glycosylation in a cell and methods of preventing or treating a cancer in a subject in need thereof.

The first invention of Group I+ is restricted based on the that the compound is not selected from the group consisting of the compounds listed in claim 1 and is restricted to a compound of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof, wherein R1 is the first shown structure; R2 is the first shown structure; R3 is the first shown structure; each occurrence of R4 is H; wherein R3 is attached para to the sulfoxide group; and pharmaceutical compositions thereof. It is believed that claims 1-4, 6, 12, and 13 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.

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. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be a compound of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof, wherein R1 is the second shown structure; R2 is the second shown structure; R3 is the second shown structure; each occurrence of R4 is C1 alkyl; wherein R3 is attached para to the sulfoxide group; and pharmaceutical compositions 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+ and 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:

The special technical features of Group I+, compounds of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof and pharmaceutical compositions thereof, are not present in Group II; and the special technical features of Group II, methods of inhibiting or disrupting N-linked glycosylation in a cell and methods of preventing or treating a cancer in a subject in need thereof, are not present in Group I+.

The Groups I+ and II formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, and R3.

The Groups I+ and II share the technical features of a compound of formula (I), or a salt, solvate, enantiomer, diastereoisomer or tautomer thereof; and a pharmaceutical composition comprising at least one pharmaceutically acceptable carrier and at least one agent selected from the group consisting of: a compound of formula (I). However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 111590126 to PubChem teaches a compound of formula (I): wherein R1 is the fifth shown structure; R2 is the third shown structure; R3 is first shown structure; each occurrence of R4 is H (Pg. 3;...see shown structure...).

Additionally, US 2006/0079557 A1 Dolle et al. teach a compound having the core structure of formula (I) (Para. [1653], compound 3.1;... see shown structure...); and a pharmaceutical composition (Claim 49; Para. [0123]) comprising at least one pharmaceutically acceptable carrier composition (Claim 49; Para. [0123]) and at least one agent selected from the group consisting of: a compound having the core structure of formula (I) composition (Claim 49; Para. [0123]; Para. [1653], compound 3.1;...see shown structure...).

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