



(51) International Patent Classification:  
*A61K 31/4725* (2006.01)

(21) International Application Number:  
PCT/US2013/039968

(22) International Filing Date:  
7 May 2013 (07.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
61/644,937 9 May 2012 (09.05.2012) 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, 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, 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, PA, 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))
- 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))

(88) Date of publication of the international search report:  
6 February 2014

(54) Title: METHODS AND COMPOSITIONS FOR TDP-43 PROTEINOPATHIES

(57) Abstract: Provided herein are methods for treating a subject suffering from a TDP-43 proteinopathy, e.g., sporadic ALS or FTD by administering to the subject a composition comprising a therapeutically effective amount of a JNK inhibitor, a MAPK inhibitor, a proteasome inhibitor, a Topoisomerase I inhibitor, a Topoisomerase II inhibitor, a HSP-90 inhibitor, a 5-HT antagonist, a CDK inhibitor, or a transcription inhibitor. The provided methods can also be used to reduce TDP-43 aggregation in human neural progenitors or neurons in neural progenitors or neurons that exhibit TDP-43 aggregates. In addition, methods are provided to identify agents that modulate (decrease or increase) TDP-43 aggregation in human neural progenitors or neurons that exhibit TDP-43 aggregates. Also provided are human induced pluripotent stem cell (hiPSC) lines generated from sporadic ALS patients, where the hiPSC lines may be differentiated into neural progenitors or neurons (e.g., motor progenitors and motor neurons) that exhibit a TDP-43 aggregate. Further provided are isolated populations of cells containing neural progenitors or neurons derived from the aforementioned hiPSC lines.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/039968

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4725 (2013.01)

USPC - 514/310

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 31/472, 31/4725 (2013.01)

USPC - 514/307, 310

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

CPC - A61K 31/472, 31/4725 (2013.01)

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

PatBase, Orbit, PubChem, Google Scholar

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                             | Relevant to claim No. |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| A         | US 2010/0331328 A1 (COLLINS et al) 30 December 2010 (30.12.2010) entire document                                                                                               | 1, 6, 9               |
| A         | WO 2010/111587 A1 (GITLER et al) 30 September 2010 (30.09.2010) entire document                                                                                                | 1, 6, 9               |
| A         | MEYEROWITZ et al. "C-Jun N-terminal kinase controls TDP-43 accumulation in stress granules induced by oxidative stress" Molecular Neurodegeneration (2011), 6:57, Pg. 1 of 22. | 1, 6, 9               |
| A         | US 5,891,855 A (FLORKIEWICZ) 06 April 1999 (06.04.1999) entire document                                                                                                        | 1, 6, 9               |
| A         | US 2006/0173020 A1 (HUANG et al) 03 August 2006 (03.08.2006) entire document                                                                                                   | 1, 6, 9               |
| A         | US 2007/0244080 A1 (FIDLER et al) 18 October 2007 (18.10.2007) entire document                                                                                                 | 1, 6, 9               |

☐ 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

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Date of the actual completion of the international search

06 December 2013

Date of mailing of the international search report

16 DEC 2013

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

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/039968

## 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, 6, 9

### 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/US2013/039968

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 1-9 and 30 are drawn to methods for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a JNK or a MAPK inhibitor of Formula (I).

Group II: Claims 10-20 are drawn to methods for identifying an agent that modulates TDP-43 aggregation, and human cell lines for use thereof.

Group III+: Claims 21-23 are drawn to methods for treating a subject suffering from a TDP-43 proteinopathy, comprising administering a therapeutically effective amount of a compound having the structure of Formula (XIV).

Group IV+: Claims 24-26 are drawn to methods for treating a subject suffering from a TDP-43 proteinopathy, comprising administering a therapeutically effective amount of a compound having the structure of Formula (XV).

Group V+: Claims 27-29 are drawn to methods for treating a subject suffering from a TDP-43 proteinopathy, comprising administering a therapeutically effective amount of a compound having the structure of Formula (XVI).

The first invention of Group I+ is restricted to a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a JNK inhibitor, wherein the inhibitor is a compound having the structure of Formula (I) or a pharmaceutically acceptable salt or solvate thereof, wherein R1 is hydrogen; R2 is hydrogen; each R3 is hydrogen; each Z is C; a is C; b is C, c is C; n is zero; and d is O. It is believed that claims 1, 6, and 9 read on this first invention and thus these claims would be searched to the extent that they read on a compound of Formula (I); or a pharmaceutically acceptable salt or solvate thereof, wherein: R1 is hydrogen; R2 is hydrogen; each R3 is hydrogen; each Z is C; a is C; b is C, c is C; n is zero; and d is O. Applicant is invited to elect additional compound(s), for each additional method to be searched in a specific combination by paying an additional fee for each set of election.

The first invention of Group III+ is restricted to a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XIV); or a pharmaceutically acceptable salt or solvate thereof. An exemplary election would be a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XIV); or a pharmaceutically acceptable salt or solvate thereof, wherein: R is the first shown ring group; R1 is a sugar species; R2 is independently OH; and W is O. It is believed that claims 21 and 22 read on this exemplary election and thus these claims would be searched to the extent that they read on a compound of Formula (XIV).

The first invention of Group IV+ is restricted to a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XV); or a pharmaceutically acceptable salt or solvate thereof. An exemplary election would be a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XV); or a pharmaceutically acceptable salt or solvate thereof, wherein: R1 is hydrogen; R2 is hydrogen; L is not present; X is O; and Y is OH. It is believed that claim 24 reads on this first named invention and thus this claim would be searched to the extent that it reads on a compound of Formula (XV).

The first invention of Group V+ is restricted to a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XVI); or a pharmaceutically acceptable salt or solvate thereof. An exemplary election would be a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (XVI); or a pharmaceutically acceptable salt or solvate thereof, wherein: R2 is hydrogen; R3 is hydrogen; R4 is hydrogen; and W is O. It is believed that claims 27 and 28 read on this exemplary election and thus these claims will be searched without fee to the extent that they read on a compound of Formula (XVI).

Applicant is invited to elect additional species of Formulas I, XIV, XV, and XVI to be searched in a specific combination for each formula by paying additional fees for each election. An exemplary election would be a method for treating a subject suffering from a TDP-43 proteinopathy, comprising administering to the subject a therapeutically effective amount of a compound having the structure of Formula (I); or a pharmaceutically acceptable salt or solvate thereof, wherein R1 is alkyl; R2 is hydrogen; each R3 is hydrogen; each Z is C; a is C; b is C, c is C; n is zero; and d is O. Additional inventions 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.

<Continued in next Extra Sheet>

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/039968

The inventions listed in Groups I through VI+ 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, methods of treatment comprising administering specific inhibitors and/or antagonist, are not present in Groups II+ through V+; the special technical features of Group II, methods for identifying an agent that modulates TDP-43 aggregation, are not present in Groups I and III+ through V+; the special technical features of Group III+, methods of treatment comprising administering a compound of Formula (XIV), are not present in Groups I, II, IV+, and VI+; the special technical features of Group IV+, methods of treatment comprising administering a compound of Formula (XV), are not present in Groups I through III+ and V+; and the special technical features of Group V+, a method of treatment comprising administering a compound of Formula (XVI), are not present in Groups I through IV+.

The Group I+ compounds of Formula (I) do not share a significant structural element that is responsible for the represented effect of treating TDP-43 proteinopathy requiring the selection of alternatives for the compound variables R1, R2, R3, Z, a-b, and n.

The Group III+ compounds of Formula (XIV) do not share a significant structural element that is responsible for the represented effect of treating TDP-43 proteinopathy requiring the selection of alternatives for the compound variables R, R1, R2, and W.

The Group IV+ compounds of Formula (XV) do not share a significant structural element that is responsible for the represented effect of treating TDP-43 proteinopathy requiring the selection of alternatives for the compound variables R1, R2, L, X, and Y.

The Group V+ compounds of Formula (XVI) do not share a significant structural element that is responsible for the represented effect of treating TDP-43 proteinopathy requiring the selection of alternatives for the compound variables R2, R3, R4, and W.

The Groups I+ through V+ share the technical features of a method for treating a subject suffering from a TDP-43 proteinopathy or modulating TDP-43 aggregation, comprising administering to the subject a therapeutically effective amount of a compound; optionally a JNK inhibitor. However, these shared technical features do not represent a contribution over the prior art. Specifically, WO 2010/111587 A1 to Gitler et al. teach a method for treating a subject suffering from a TDP-43 proteinopathy or modulating TDP-43 aggregation, comprising administering to the subject a therapeutically effective amount of a compound (see Pgs. 2-3 Lns. 23-32 and 1-7, methods are provided for the treatment and prevention of proteinopathy disorders. The present inventor has identified a variety of TDP-43 toxicity modulators via overexpression assays and deletion assays. The modulators act to suppress or enhance TDP-43 mediated toxicity and/or aberrant protein aggregation in TDP-43 expressing cells...method for treating or inhibiting development of a proteinopathy in a subject in need thereof comprises administering an effective amount of a pharmaceutical composition comprising a therapeutic amount of an agent which inhibits expression or activity of at least one gene). Further, "C-Jun N-terminal kinase controls TDP-43 accumulation in stress granules induced by oxidative stress" to Meyerowitz et al. teach administering to the subject or contacting a population of cells with a therapeutically effective amount of a JNK inhibitor (see Abstract, co-localization of TDP-43 with SGs could be fully prevented by inhibition of c-Jun N-terminal kinase (JNK)...JNK inhibition also inhibited TDP-43 SG localization in cells acutely treated with sodium arsenite and reduced the number of aggregates per cell in cultures transfected with C-terminal TDP-43).

The Group I+ claims share the technical features of a compound of Formula (I): or a pharmaceutically acceptable salt or solvate thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2010/0331328 A1 to Collins et al. teach a compound of Formula (I): or a pharmaceutically acceptable salt or solvate thereof, wherein: R1 is hydrogen; R2 is hydrogen; each R3 is not present or hydrogen; each Z is C; a is C; b is N; c is C; n is one; and d is N (see Para. [0041], ...Isouquinolin-3-yl-pyrazin- 2-yl-amine...).

The Group III+ claims share the technical features of a compound of Formula (XIV): or a pharmaceutically acceptable salt or solvate thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 5,891,855 A to Florkiewicz teaches a compound of Formula (XIV): or a pharmaceutically acceptable salt or solvate thereof, wherein: R is the first shown ring group; R1 is a sugar species; R2 is independently selected from OH, alkyl, and hydrogen; and W is O (see Fig 1A, formulas I and II; Col. 2 Lns. 33-34 and 59-67, FIG. 1 is a drawing of the general structure of the aglycone nucleus of various cardiac glycosides..."Cardiac glycoside" refers to a group of compounds which are structurally related. Structurally, these compounds are derived from the cyclopentanoperhydro-phenanthrene nucleus characteristic of steroid compounds, have a five-membered unsaturated lactone ring or a six-membered doubly unsaturated lactone ring at C17 of ring D...a hydroxyl group at C3 in ring A for joining by an ether linkage to one or more sugar residues...).

The Group IV+ claims share the technical features of a compound of Formula (XV): or a pharmaceutically acceptable salt or solvate thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2006/0173020 A1 to Huang et al. teach a compound of Formula (XVa) (from instant claim 25): or a pharmaceutically acceptable salt or solvate thereof, wherein: R1 is SO2Rx; R2 is halogen; each Rx is substituted amino; and L is -C(O)- (see Para. [0116], another embodiment of this invention, there is provided a compound of formula (III) shown).

The Group V+ claims share the technical features of a compound of Formula (XVI): or a pharmaceutically acceptable salt or solvate thereof. However, these shared technical features do not represent a contribution over the prior art. Specifically, US 2007/0244080 A1 to Fidler et al. teach a compound of Formula (XVI): or a pharmaceutically acceptable salt or solvate thereof, wherein: R2 is alkyl; R3R4 taken together is =O; and W is O (see Paras. [0058]-[0059], ...a solution of triptonide (designated PG492)).

Since none of the special technical features of the Groups I+ through V+ inventions are found in more than one of the inventions, unity is lacking.