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— *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))*

[Continued on next page]

(54) Title: COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING NEURODEGENERATIVE DISORDERS

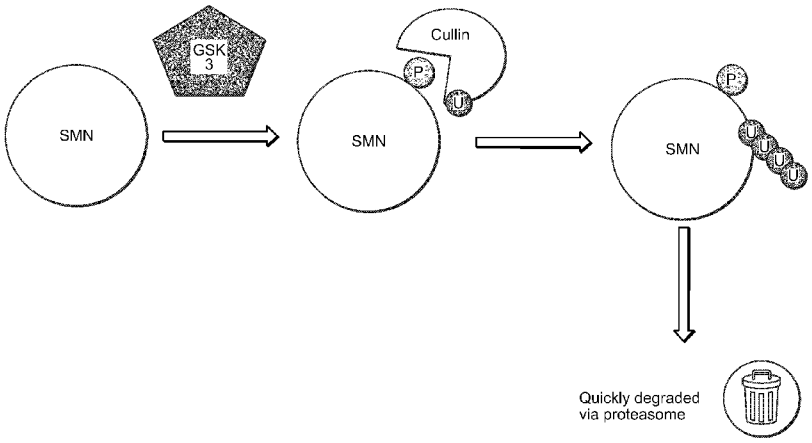

FIG. 1

(57) Abstract: The disclosure provides compounds, compositions, and methods for promoting motor neuron survival, and for treating or preventing neurodegenerative disorders, such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS). In accordance with an embodiment of the present invention, a method of regulating survival of motor neuron (SMN) protein levels in a cell is provided. The method includes contacting the cell with an effective amount of an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the cell and an effective amount of an agent which increases the level of SM7N protein, thereby regulating SMN protein levels in the cell.

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11 August 2016

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A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/519; A61K 45/06; A61P 25/28 (2016.01)
CPC - A61K 31/165; A61K 31/519; A61K 45/06 (2016.05)
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 31/519; A61K 45/06; A61P 25/28 (2016.01)
CPC - A61K 31/165; A61K 31/519; A61K 45/06 (2016.05)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/375; 514/183; 514/265.1 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase, Google Patents, PubMed, Google.

Search terms used: MLN9424 Nedd8 SMN survival motor neuron protein neurodegeneration administer neural cells

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013/188881 A1 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE et al) 19 December 2013 (19.12.2013) entire document	1, 8-14, 21-26, 33-36, 43-50
A	MILHOLLEN et al. "MLN4924, a NEDD8-activating enzyme inhibitor, is active in diffuse large B-cell lymphoma models: rationale for treatment of NF- B –dependent lymphoma," Blood, 02 September 2010 (02.09.2010), Vol. 116, No. 9, Pgs. 1515-1523. entire document	1, 8-14, 21-26, 33-36, 43-50
A	US 2014/0249167 A1 (MILLENIUM PHARMACEUTICALS INC et al) 04 September 2014 (04.09.2014) entire document	1, 8-14, 21-26, 33-36, 43-50
A	SWORDS et al. "Inhibition of NEDD8-activating enzyme: a novel approach for the treatment of acute myeloid leukemia," Blood, 06 May 2010 (06.05.2010), Vol. 115, No. 18, Pgs. 3796-3800. entire document	1, 8-14, 21-26, 33-36, 43-50
A	ZHAO et al. "The NEDD8-activating enzyme inhibitor, MLN4924, cooperates with TRAIL to augment apoptosis through facilitating c-FLIP degradation in head and neck cancer cells," Mol. Cancer Ther., 01 December 2012 (01.12.2012), Vol. 10, No. 12, Pgs. 2415-2425. entire document	1, 8-14, 21-26, 33-36, 43-50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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
25 May 2016	20 JUN 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2015/065885

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(s).

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, 8-14, 21-26, 33-36, and 43-50 restricted to an agent selected to be ((1S,2S,4R)-4-(4-(((S)-2,3- dihydro-1H-inden-1-yl) amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-hydroxycyclopentyl) methyl sulfamate (MLN4924).

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

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Continued from Box No. 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 1-50 are drawn to an agent which inhibits the level or activity of Nedd8 activating enzyme, and methods comprising the same.

The first invention of Group I+ is restricted to an agent which inhibits the level or activity of Nedd8 activating enzyme, and methods comprising the same, wherein the agent is selected to be ((1S,2S,4R)-4-(4-(((S)-2,3-dihydro-1H-inden-1-yl)amino)-7H-pyrrolo[2,3-d] pyrimidin-7-yl)-2-hydroxycyclopentyl) methyl sulfamate (MLN4924). It is believed that claims 1, 8-14, 21-26, 33-36, and 43-50 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the MLN4924.

Applicant is invited to elect additional agents with specified chemical structure to be searched in a specific combination by paying additional fee for each set of election. An exemplary election would be an agent which inhibits the level or activity of Nedd8 activating enzyme, and methods comprising the same, wherein the agent is selected to be Apicidin ([cyclo-L-(2-amino- 8-oxodecanoyl)-L-(N -methoxy-tryptophan)-L-isoleucyl-D-pipecolinyll). Additional agents with specified chemical structure 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+ 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 Groups I+ formulas do not share a significant structural element responsible for inhibiting the level or activity of Nedd8 activating enzyme requiring the selection of alternatives for the agent, where "the agent which inhibits the level or activity of NAE is a compound of formula (I): (See structure of claim 9 in the instant application) wherein: Ring A is a 6-membered nitrogen-containing heteroaryl ring, optionally fused to a 5- or 6-membered aryl, heteroaryl, cycloaliphatic or heterocyclic ring, wherein either or both rings is optionally substituted and one ring nitrogen atom is optionally oxidized or Ring A is selected from the group consisting of: (see structures in claim 9 of the instant application), W is CH2 , CHF, CH2, CH(R1), CH(R1), NH, N(R), O, S, or -NHC(O)-; R' is C1-4 aliphatic or C1-4 fluoroaliphatic; or R1 is a C2-4 alkylene chain that is attached to a ring position on Ring A to form a 5-, 6-, or 7- membered fused ring, wherein the alkylene chain optionally is substituted with C1-4 aliphatic, C1-4 fluoroaliphatic, -O, -CN, or -C(O)N(R4)2; X is CH2, CHF, CH2, NH, or O; Y is -O-, -S-, or -C(Rm)(Rn)-; Ra is selected from the group consisting of hydrogen, fluoro, CN, N3, OR N(R4)2, NR4CO2R6, -NR4C(O)R5, -C(O)N(R4)2, -(O)R5, -C(O)N(R4)2, -OC(O)R5, -OCO2R6, or a C1-4 aliphatic or C1-4 fluoroaliphatic optionally substituted with one or two substituents independently selected from the group consisting of -OR5x, -N(R4x)(R4y), -CO2R5x, or -C(O)N(R4x)(R44y); or Ra and Rc together form a bond; Rb is selected from the group consisting of hydrogen, fluoro, C1-4 aliphatic, and C1-4 fluoroaliphatic; Rc is selected from the group consisting of hydrogen, fluoro, CN, N3, OR5, N(R4)2, NR4CO2R6, -NR4C(O)R5, -C(O)N(R4)2, -(O)R5, -C(O)N(R4)2, -OC(O)R5, -OCO2R6, or a C1-4 aliphatic or C1-4 fluoroaliphatic optionally substituted with one or two substituents independently selected from the group consisting of -OR5x, -N(R4x)(R4y), -CO2R5x, or -C(O)N(R4x)(R44y); or Ra and Rc together form a bond; Rd is selected from the group consisting of hydrogen, fluoro, C1-4 aliphatic, and C1-4 fluoroaliphatic; Re is hydrogen, or C1-4 aliphatic; or Re, taken together with one Rf and the intervening carbon atoms, forms a 3- to 6-membered spirocyclic ring; or Re, taken together with Rm and the intervening carbon atoms, forms a fused cyclopropane ring, which is optionally substituted with one or two substituents independently selected from fluoro or C1-4 aliphatic; Re' is hydrogen or C1-4 aliphatic; or Re', taken together with Rm and the intervening carbon atoms, forms a fused cyclopropane ring, which is optionally substituted with one or two substituents independently selected from fluoro or C1-4 aliphatic; each Rf is independently hydrogen, fluoro, C1-4 aliphatic, or C1-4 fluoroaliphatic; or two Rf taken together form =O; or two Rf, taken together with the carbon atom to which they are attached, form a 3- to 6-membered carbocyclic ring; or one Rf, taken together with Re and the intervening carbon atoms, forms a 3- to 6-membered spirocyclic ring; Rm is hydrogen, fluoro, -N(R4)2 , or an optionally substituted C1-4 aliphatic group; or Rm and Rm together form =O or =C(R5)2; or Rm and Re, taken together with the intervening carbon atoms, form a fused cyclopropane ring, which is optionally substituted with one or two substituents independently selected from fluoro or C1-4 aliphatic; or Rm and Re', taken together with the intervening carbon atoms, form a fused cyclopropane ring, which is optionally substituted with one or two substituents independently selected from fluoro or C1-4 aliphatic; Rn is hydrogen, fluoro, or an optionally substituted C1-4 aliphatic group; or Rm and Rn together form =O or =C(R5)2; each R4 independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group; or two R4 on the same nitrogen atom, taken together with the nitrogen atom, form an optionally substituted 4 to 8-membered heterocyclyl ring having, in addition to the nitrogen atom, 0-2 ring heteroatoms independently selected from N, O, and S; R4x is hydrogen, C1-4 alkyl, C1-4 fluoroalkyl, or C6-10ar (C1-4)alkyl, the aryl portion of which can be optionally substituted; R4y is hydrogen, C1-4 alkyl, C1-4 fluoroalkyl, C6-10ar(C1-4)alkyl, the aryl portion of which can be optionally substituted, or an optionally substituted 5- or 6-membered aryl, heteroaryl, or heterocyclyl ring; or R4x and R4y, taken together with the nitrogen atom to which they are attached, form an optionally substituted 4- to 8-membered heterocyclyl ring having, in addition to the nitrogen atom, 0-2 ring heteroatoms independently selected from N, O, and S; and each R5 independently is hydrogen or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl group; each R5x independently is hydrogen, C1-4 alkyl, C1-4 fluoroalkyl, or an optionally substituted C6-10aryl or C6-10ar(C1-4)alkyl; each R6 independently is an optionally substituted aliphatic, aryl, or heteroaryl group; Rg is hydrogen, halo, -NO2, -CN, -C(R5)=C(R5)2 , -C=C-R, -OR5, -SR6, -S(O) R6, -SO2R6 , -SO2N(R4)2, -N(R4)2 , -NR4C(O)R5, -NR4C(O)N(R4)2, -N(R4)C=NR4)-N(R4)2, -N(R4)C(=NR4)-R6, -NR4CO2R6, -N (R4)SO2R6, -N(R4)SO2N(R4)2, -O-C(O)R5, -OCO2R6, -OC(O)N(R4)2, -C(O)R5, -CO2R5, -C(O)N(R4)2, -C(O)N(R4)-OR5, -C(O)N(R4) C(=NR4)-N(R4)2, -N(R4)C(=NR4)-N(R4)-C(O)R5, C(=NR4)-N(R4)2, -C(=NR4)-OR5, -N(R4)_-N(R) 2 , -N(R 4)-OR5, C(=NR 4)-N(R 4)-OR5, -C(R6)=N-OR5, or an optionally substituted aliphatic, aryl, heteroaryl, or heterocyclyl; each Rh independently is hydrogen, halo, -CN-, -OR5, -N(R4)2, -SR6, or an optionally substituted C1-4 aliphatic group; each Rj is hydrogen, -OR5, -SR6, -N(R)2, or an optionally substituted aliphatic, aryl, or heteroaryl group; Rk is hydrogen, halo, -OR5 , -SR6, -N(R4)+, or an optionally substituted C1-4 aliphatic group; m is 1, 2, or 3; and pharmaceutically acceptable salts thereof".

INTERNATIONAL SEARCH REPORT

International application No.
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The Groups I+ share the technical features of A method of regulating survival of motor neuron (SMN) protein levels in a cell, comprising contacting the cell with an effective amount of an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the cell and an effective amount of an agent which increases the level of SMN protein, thereby regulating SMN protein levels in the cell; method of promoting cell survival in a subject in need thereof by regulating the overall levels of SMN protein in the subject, comprising administering to a subject an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the subject's cells and an effective amount of an agent which increases the level of SMN protein, thereby promoting cell survival in the subject; a method of treating or preventing a neurodegenerative disorder in a subject in need thereof, comprising administering to the subject at least one agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) and an effective amount of an agent which increases the level of SMN protein. However, these shared technical features do not represent a contribution over the prior art.

Specifically, WO 2013/188881 A1 to President and Fellows of Harvard College et al. discloses a method of regulating survival of motor neuron (SMN) protein levels in a cell (The disclosure provides compounds, compositions, and methods for promoting motor neuron survival,, Abstract), comprising contacting the cell with an effective amount of an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the cell and an effective amount of an agent which increases the level of SMN protein, thereby regulating SMN protein levels in the cell (In some aspects, the disclosure provides a method of regulating survival of motor neuron (SMN) protein levels in a cell, comprising contacting the cell with an effective amount of an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the cell, thereby regulating SMN protein levels in the cell, Para. [0007]; any agent which increases the levels of SMN protein, stabilizes levels of SMN protein, Para. [0027]); method of promoting cell survival in a subject in need thereof by regulating the overall levels of SMN protein in the subject, comprising administering to a subject an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the subject's cells and an effective amount of an agent which increases the level of SMN protein, thereby promoting cell survival in the subject (In some aspects, the disclosure provides a method of regulating survival of motor neuron (SMN) protein levels in a cell, comprising contacting the cell with an effective amount of an agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) in the cell, thereby regulating SMN protein levels in the cell, Para. [0007]; any agent which increases the levels of SMN protein, stabilizes levels of SMN protein, Para. [0027]); a method of treating or preventing a neurodegenerative disorder in a subject in need thereof, comprising administering to the subject at least one agent which inhibits the level or activity of Nedd8 activating enzyme (NAE) and an effective amount of an agent which increases the level of SMN protein (Accordingly, in an aspect, provided herein is a method of treating or preventing a disorder characterized by degradation of SMN protein in a subject in need thereof, comprising administering to the subject an effective amount of at least one agent which regulates degradation of SMN protein in a subject...In some embodiments, the disorder characterized by degradation of SMN protein is a neurodegenerative disorder, Para. [0081]).

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