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30 December 2009

(54) Title: INHIBITION OF DCPS

(57) Abstract: The disclosure relates to methods and compositions (e.g., compounds and pharmaceutical compositions thereof) useful for increasing expression of SMN in a cell (e.g., *in vitro* or *in vivo*). As a deficiency in SMN can result in the development of an SMA condition in a subject, the methods and compositions described herein can also be used to, e.g., treat, or prevent, an SMA condition in a subject.



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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/38108

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(8) - A61K 31/517(2009.01) USPC - 514/266.1; 514/266.21 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC (8) - A61K 31/517(2009.01) USPC - 514/266.1; 514/266.21 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC - 514/234.5; 514/252.17; 514/266.2; 514/266.4; 514/313; 544/245; 544/291; 544/119; 544/253; 544/284; 544/293; 546/159 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google: SMN, survival motor neuron, DcpS, scavenger decapping, inhibitor, 2,4-diaminoquinazoline, atrophy		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Thurmond et al. Synthesis and biological evaluation of novel 2,4-diaminoquinazoline derivatives as SMN2 promoter activators for the potential treatment of spinal muscular atrophy. J Med Chem. 14 Feb 2008; 51(3):449-69. Epub 2008 Jan 19; pg 449, left col, 1st para & right col., 2nd para; pg 450, left col, 2nd to 3rd para, Fig 1; pg 452, right col, 2nd para; p. 453, Table 3; p. 457, left col., 1st para; p. 458, right col., 2nd para; p. 459, right col., 1st para	1-6, 9-25
Y	Liu et al. The scavenger mRNA decapping enzyme DcpS is a member of the HIT family of pyrophosphatases. EMBO J. 2002; 21(17):4699-4708; pg 4701, left col, 2nd para, right col, 1st para; pg 4702, legend of Fig 3; pg 4705, Fig 6A	1-6, 9-25
A,P	US 2009/0042900 A1 (Singh, et al.) 12 Feb 2009 (12.02.2009)	1-6, 9-25
A	US 2005/0288314 A1 (Singh, et al.) 29 December 2005 (29.12.2005)	1-6, 9-25
A	Davies et al. Spinal muscular atrophies-distinctions and therapeutic progress. Drugs of the Future 2006, 31(4): 365-371	1-6, 9-25
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/>		
* 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 6 August 2009 (06.08.2009)		Date of mailing of the international search report <b>20 AUG 2009</b>
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: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/38108

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:

Group I: claims 1-6, 8-25, drawn to a administering to the subject a compound that inhibits DcpS, wherein claims 6 and 25 are limited to the compound of the claimed structural formula, wherein X and Y are each CH.  
[NOTE: Claim 8, drawn to the DepS inhibitor comprising the structure of Cpd.1 is outside of the scope of Group I and therefore was not searched.]

Group II+: claims 1-27, drawn to a administering to the subject a compound that inhibits DcpS, wherein claims 6 and 25 are limited to the compound of the claimed structural formula, wherein X and Y are each independently CH or N, but not both CH.

\*\*\*\*\* SEE SUPPLEMENTAL PAGE TO CONTINUE \*\*\*\*\*

- 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, 9-25

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.

\*\*\*\*\* SUPPLEMENTAL PAGE \*\*\*\*\*

The inventions listed as Groups I-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 feature of the invention listed as Groups I-II+ is the specific DepS inhibitor compound recited therein. Said compounds would be regarded as having the same or corresponding technical feature if they had a common property or activity, and shared a significant structural element that is essential to the common property or activity and is an improvement over prior art. While said compounds do share the common property of specifically inhibiting DepS, prior art teaches their shared significant structural element. Specifically, the article entitled "Spinal muscular atrophies-distinctions and therapeutic progress" by Davies et al. (Drugs of the Future 2006, 31(4): 365-371) discloses "compounds that could be useful as SMN2 promoters (12), and ... 2,4-diaminoquinazolines that increase the production of SMN2" (pg 367, col 2). In addition, Davies et al. discloses 5-(4-Methylphenoxy)quinazoline-2,4-diamine (pg 368, Table II) that anticipates a compound of claim 6 as follows:

U is O;

n is 0;

X and Y are CH;

R10, R11, R12, R13 are H,

Q is -CR14R15-, wherein R14 and R15 are H,

R1 is H.

Thus, the shared significant structural element is an improvement over the prior art, and hence, there is no disclosure of the same or corresponding technical feature. Therefore, unity of invention between Groups I and II+ is lacking.

Similarly, the special technical feature of the invention listed as Groups II+ is the specific DepS inhibitor compound recited therein. Said compounds would be regarded as having the same or corresponding technical feature if they had a common property or activity, and shared a significant structural element that is essential to the common property or activity and is an improvement over prior art. While said compounds do share the common property of specifically inhibiting DepS, prior art teaches their shared significant structural element. Specifically, a PubChem entry DD1 (CID 23729147) (19 Feb 2008) [Retrieved from the Internet 27 May 2009:

<[http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=23729147&loc=ec\\_rcs#Synonyms](http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=23729147&loc=ec_rcs#Synonyms)>) discloses

5-[[1-[(2-fluorophenyl)methyl]piperidin-4-yl]methoxy]quinazoline-2,4-diamine, i.e. the claimed compound Cpd.1. Thus, the shared significant structural element is an improvement over the prior art, and hence, there is no disclosure of the same or corresponding technical feature. Therefore, unity of invention between Groups II+ is lacking.

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