



(51) International Patent Classification:

A61K 38/45 (2006.01) A61K 31/133 (2006.01)
A61K 39/395 (2006.01) A61P 31/12 (2006.01)
A61K 48/00 (2006.01) A61P 31/00 (2006.01)

(21) International Application Number:

PCT/US2012/040115

(22) International Filing Date:

31 May 2012 (31.05.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/519,881 1 June 2011 (01.06.2011) US

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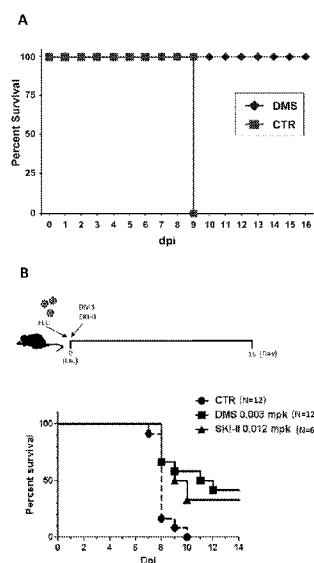
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, 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, 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).

[Continued on next page]

(54) Title: MODULATION OF SPHINGOSINE 1-PHOSPHATE METABOLIZING ENZYMES FOR THE TREATMENT OF NEGATIVE-STRAND RNA VIRUS INFECTIONS

Reduced mortality of influenza virus-infected mice by SK inhibitor treatment



(57) Abstract: The present invention relates to compounds and methods for the prevention or treatment of infections by negative strand RNA viruses, such as influenza virus and measles virus, wherein said compounds delay or inhibit viral replication by modulating the level or activity of a polypeptide involved in the synthesis or degradation of sphingosine-1-phosphate (S1P) in a cell, tissue, or subject. The methods involve administration of one or more compounds which modulate the level of gene expression, where the gene encodes a polypeptide involved in regulating the metabolic level of S1P, or modulate the level or activity of a polypeptide involved in regulating the metabolic level of S1P, such as sphingosine kinase (SK) and S1P lyase (SPL). Exemplary methods are directed towards reducing the level of S1P by reducing the level or activity of one or more SKs, increasing the level or activity of one or more SPLs, or a combination of both steps.



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))*

— *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:
21 March 2013

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/040115**A. CLASSIFICATION OF SUBJECT MATTER****A61K 38/45(2006.01)i, A61K 39/395(2006.01)i, A61K 48/00(2006.01)i, A61K 31/133(2006.01)i, A61P 31/12(2006.01)i, A61P 31/00(2006.01)i**

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)

A61K 38/45; A61P 31/16; A61K 31/664

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: negative-strand RNA virus, Sphingosine-1-phosphate (S1P), sphingosine kinase(SK), Orthomyxoviridae, Paramyxoviridae, influenza virus, measles virus, infection

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SEO, Y. J., et al., Sphingosine 1-phosphate-metabolizing enzymes control influenza virus propagation and viral cytopathogenicity. J. Virol. 84(16): 8124-8131 (Epub. 2 Jun. 2010)	31-34,37-60
A	See abstract and result	35,36
X	MONICK, M. M., et al., Sphingosine kinase mediates activation of extracellular signal-related kinase and Akt by respiratory syncytial virus. Am. J. Respir. Cell Mol. Biol. 30(6): 844-852 (Epub. 23 Jan. 2004)	31,32,35,37-60
Y	See abstract, introduction and figure 7	36
A		33,34
Y	PALESE, P., et al., Negative-strand RNA viruses: genetic engineering and applications. Proc. Natl. Acad. Sci. U. S. A. 93(21): 11354-11358 (15 Oct. 1996)	36
A	See abstract	31-35,37-60

☒ 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 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

21 JANUARY 2013 (21.01.2013)

Date of mailing of the international search report

22 JANUARY 2013 (22.01.2013)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/040115**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.: 1-30, 61-90
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 1-30, 61-90 pertain to methods for treatment of the human body by surgery or therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
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:

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 an additional fee, this Authority did not invite payment of any additional fee.
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.:

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/US2012/040115

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SIOW, D. L., et al., Sphingosine kinase localization in the control of sphingolipid metabolism. Adv. Enzyme Regul. 51(1): 229-244 (Epub. 12 Nov. 2010) See abstract	31-60
A	US 2009-0312291 A1 (KAWAKAMI, HIROSHI) 17 Dec. 2009 See the whole document	31-60

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/040115

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009-0312291 A1	17.12.2009	AU 2007-279674 A1	07.02.2008
		CA 2660120 A1	07.02.2008
		CN 101505767 A	12.08.2009
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