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[Continued on next page]

(54) Title: SYNAPTOJANIN-2 INHIBITORS FOR USE IN THE TREATMENT OF CANCER

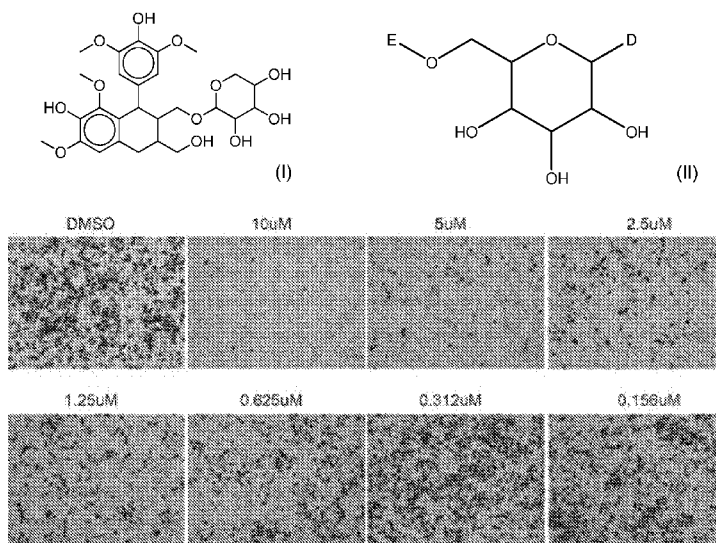


Figure 20B

(57) Abstract: Disclosed herein are synaptojanin-2 inhibitors, and novel methods and uses utilizing same for preventing tumor metastasis, treating cancer or inhibiting synaptojanin-2. Compounds disclosed herein include chlorhexidine and pyrvinium, the compound having the formula: (I) and compounds characterized by the general formula: X-L-[(Y)i-(Z)j]-(L-X)k and/or by the general formula: (II) wherein L, X, Y, Z, D, E, i, j and k are as defined herein.





Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

— *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))*

Published:

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(88) Date of publication of the international search report:

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K45/06 A61K31/05 A61K31/12 A61K31/155 A61K31/216
A61K31/235 A61K31/352 A61K31/353 A61K31/4709 A61K31/7024
A61K31/7028 A61K31/7032 A61K31/7034 A61K31/7048 A61P35/00

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 A61P

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

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

EPO-Internal, CHEM ABS Data, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 2014/083567 A2 (YEDA RES & DEV [IL]) 5 June 2014 (2014-06-05) abstract page 13, line 30 - line 32 page 15, line 11 - page 17, line 1 page 36, line 18 - line 20; examples 8,9 claims 1-7; table 2 ----- -/--	1-29, 32-34, 42,43, 46-50



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

7 April 2015

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/066404

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 119 434 A1 (INST NAT SANTE RECH MED [FR]) 18 November 2009 (2009-11-18) abstract page 3, paragraphs 13,19,21; claims; example 3	1,3,5,7, 9-11,13, 15,17, 19-24, 26,29, 32-34, 42,43, 46,48
X	TANIMURA S ET AL: "Suppression of tumor cell invasiveness by hydrolyzable tannins (plant polyphenols) via the inhibition of matrix metalloproteinase-2/-9 activity", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, ACADEMIC PRESS INC. ORLANDO, FL, US, vol. 330, no. 4, 20 May 2005 (2005-05-20), pages 1306-1313, XP004844871, ISSN: 0006-291X, DOI: 10.1016/J.BBRC.2005.03.116 abstract page 1309, right-hand column, last paragraph - page 1310, left-hand column, paragraph 1; table 1	1,3,5,7, 9-11,13, 15,17, 19-24, 26,29, 32-34, 42,43, 46-48
X	KR 2010 0138398 A (UNIV KONKUK IND COOP CORP [KR]) 31 December 2010 (2010-12-31) page 7, paragraph 17; claims	1,5,11, 15, 19-24, 29, 32-34, 42,43, 46-48
X	JP 2006 008523 A (LB MAPLE TREAT INC; MIC KK) 12 January 2006 (2006-01-12) abstract compound 10; page 6 -/--	1,3,5,7, 9-11,13, 15,17, 19-24, 26,29, 32-34, 42,43, 46-48

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/066404

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	-& DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 13 January 2006 (2006-01-13), ARIHARA, SHIGENOBU ET AL: "Phenol compounds from maple plant as health foods for prevention and treatment of diabetes, obesity and cancer", XP002738087, retrieved from STN Database accession no. 2006:31344 abstract -----	
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 5 April 2010 (2010-04-05), CUI, CHENGBIN ET AL: "Extraction method of galloyl glucopyranose compounds from Chinese medicine Choerospondias and its application as antitumor and anti-hypoxic agents", XP002738088, retrieved from STN Database accession no. 2010:418008 abstract see Rn=23363-08-8 -----	1,3,5,7, 9-11,13, 15,17, 19-24, 26,29, 32-34, 42,43, 46-48
X	ITO HIDEYUKI ET AL: "Anti-tumor promoting activity of polyphenols from Cowania mexicana and Continue and Coleogyne ramosissima", CANCER LETTERS, NEW YORK, NY, US, vol. 143, no. 1, 23 August 1999 (1999-08-23), pages 5-13, XP009147210, ISSN: 0304-3835, DOI: 10.1016/S0304-3835(99)00160-3 [retrieved on 1999-07-23] abstract; figure 2 page 10, left-hand column, last paragraph - page 12, left-hand column, last paragraph -----	1-3,5-7, 9-13, 15-17, 19-26, 29, 32-34, 42,43, 46-50
X	DATABASE WPI Week 201276 Thomson Scientific, London, GB; AN 2012-N95709 XP002738089, -& WO 2012/144711 A2 (KOREA INST SCI & TECHNOLOGY) 26 October 2012 (2012-10-26) abstract page 7, paragraph 55; claims -----	1-3,5-7, 9-13, 15-17, 19-26, 29, 32-34, 42,43, 46-50

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/066404

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FENG NI ET AL: "Flavonoid Ampelopsin Inhibits the Growth and Metastasis of Prostate Cancer In Vitro and in Mice", PLOS ONE, vol. 7, no. 6, E38802, 5 June 2012 (2012-06-05), pages 1-9, XP055098872, ISSN: 1932-6203, DOI: 10.1371/journal.pone.0038802 the whole document	1
A	Ya-Yu Chuang ET AL: "Role of Synaptojanin 2 in Glioma Cell Migration and Invasion Updated version", Cancer Research, 15 November 2004 (2004-11-15), pages 8271-8275, XP055098695, Retrieved from the Internet: URL:http://cancerres.aacrjournals.org/content/64/22/8271.full.pdf [retrieved on 2014-01-27] the whole document	1-29, 32-34, 42,43, 46-50
A	BODMER ALEXANDRE ET AL: "Anticorps et tumeurs solides: cibles établies et pistes prometteuses // The potential of monoclonal antibodies in cancer : established trastuzumab and cetuximab and promising targets IGF-1R and c-MET", M/S MEDECINE SCIENCES, vol. 25, no. 12, 1 December 2009 (2009-12-01), pages 1090-1098, XP009141211, SOCIETE DES PERIODIQUES FLAMMARION, PARIS, FR ISSN: 0767-0974 the whole document	1-29, 32-34, 42,43, 46-50
A	PONOU B K ET AL: "Dimeric antioxidant and cytotoxic triterpenoid saponins from Terminalia ivorensis A. Chev", PHYTOCHEMISTRY, vol. 71, no. 17-18, 1 December 2010 (2010-12-01), pages 2108-2115, XP027491126, PERGAMON PRESS, GB ISSN: 0031-9422, DOI: 10.1016/J.PHYTOCHEM.2010.08.020 [retrieved on 2010-11-11] abstract; figure 1 page 2113, right-hand column, paragraph 3; table 5	1-29, 32-34, 42,43, 46-50

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/066404

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 additional 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 an 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.:
2, 6, 12, 16, 25, 42, 49, 50(completely); 1, 3-5, 7-11, 13-15, 17-24, 26-29
32-34, 43, 46-48(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2, 6, 12, 16, 25, 42, 49, 50(completely); 1, 3-5, 7-11, 13-15, 17-24, 26-29, 32-34, 43, 46-48(partially)

Compound of formula I, wherein Z is a monosaccharide or disaccharide moiety (j is 1) selected from the compounds of formula III and the compounds 2,5,6,7,9,12 to 16,19 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

2. claims: 30, 31, 35-41(completely); 1, 3, 5, 7, 9-11, 13, 15, 17, 19-24, 26, 28, 29, 32-34, 43, 46-48(partially)

Compound of formula I, wherein Y is a bicyclic moiety of formula II (i is 1) selected from the compounds 1,3,4,10,11,22,24 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

3. claims: 1, 3, 5, 7, 9-11, 13, 15, 17, 19-24, 26, 28, 29, 32-34, 43-45(all partially)

Compound 8 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

4. claims: 1, 3-5, 7-11, 13-15, 17-24, 26-29, 32-34, 43, 44(all partially)

Compound 17 of Table 1 (chlorhexidine) for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

5. claims: 1, 3-5, 7-11, 13-15, 17-24, 26-29, 32-34, 43, 44(all partially)

Compound 18 of Table 1 (pyrvinium pamoate) for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. claims: 1, 3, 5, 7, 9-11, 13, 15, 17, 19-24, 26, 28, 29, 32-34, 43, 44(all partially)

Compound 20 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

7. claims: 1, 3, 5, 7, 9-11, 13, 15, 17, 19-24, 26, 28, 29, 33, 34, 43, 44, 47, 48(all partially)

Compound 21 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

8. claims: 1, 3, 5, 7, 9-11, 13, 15, 17, 19-24, 26, 28, 29, 32-34, 43-45(all partially)

Compound 23 of Table 1 for preventing tumor metastasis; for treating cancer in combination with an inhibitor of a cell surface receptor associated with the onset or progression of cancer; for inhibiting synaptojanin-2.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/066404

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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