



(43) International Publication Date
18 September 2014 (18.09.2014)

- (51) International Patent Classification:
G01N 33/574 (2006.01) *A61P 35/00* (2006.01)
- (21) International Application Number:
PCT/IB2014/059585
- (22) International Filing Date:
10 March 2014 (10.03.2014)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
61/776,334 11 March 2013 (11.03.2013) US
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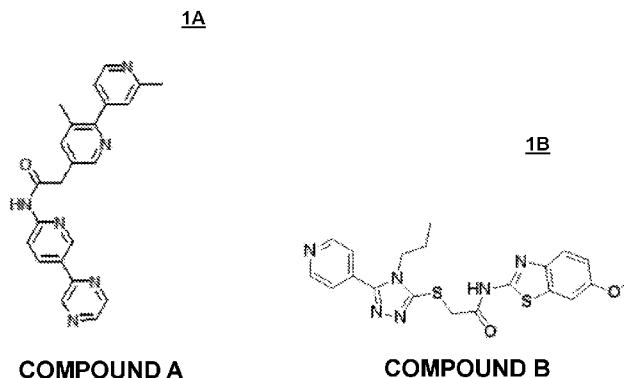
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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, 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, SA, 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,

(54) Title: MARKERS ASSOCIATED WITH WNT INHIBITORS

FIGURE 1



(57) Abstract: The invention provides methods of monitoring differential gene expression of biomarkers to determine patient sensitivity to Wnt inhibitor, methods of determining the sensitivity of a cell to an Wnt inhibitor by measuring biomarkers, methods of screening for candidate Wnt inhibitor, Wnt inhibitor for use in head and neck squamous cell carcinoma.



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, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

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

27 November 2014

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

INTERNATIONAL SEARCH REPORT

International application No PCT/IB2014/059585
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A. CLASSIFICATION OF SUBJECT MATTER
 INV. G01N33/574 A61P35/00
 ADD.

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)
G01N

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, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>J. LIU ET AL: "PD08-11: Targeting Porcupine, a Critical Node for Wnt Signalling in Cancer.", CANCER RESEARCH, vol. 71, no. 24 Supplement, 15 December 2011 (2011-12-15), pages PD08-11, XP055061279, ISSN: 0008-5472, DOI: 10.1158/0008-5472.SABCS11-PD08-11 abstract</p> <p style="text-align: center;">----- -/--</p>	<p>2,5-8, 11-19, 21-26, 32-45</p>



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

6 June 2014

Date of mailing of the international search report

09/09/2014

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2014/059585

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.:

6, 7, 18, 19, 24, 25(completely); 1-5, 8, 9, 11-17, 21-23, 26-28
32-45(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: 6, 7, 18, 19, 24, 25(completely); 1-5, 8, 9, 11-17, 21-23, 26-28, 32-45(partially)

Methods, entities and uses relating Notch 1-3 to cancer treatment/sensitivity to cancer treatment with Wnt inhibitors.

2. claims: 1-5, 8, 9, 11-17, 21-23, 26-28, 32-45(all partially)

Methods, entities and uses relating Notch 2 to cancer treatment/sensitivity to cancer treatment with Wnt inhibitors.

3. claims: 1-5, 8, 9, 11-17, 21-23, 26-28, 32-45(all partially)

Methods, entities and uses relating Notch 3 to cancer treatment/sensitivity to cancer treatment with Wnt inhibitors.

- 4-24. claims: 1-5, 8-17, 20-23, 26-28, 32-45(all partially)

Methods, entities and uses relating AXIN2 (invention 2), LEF1 (invention 3), ... up to ... FAT1 (invention 22) to cancer treatment/sensitivity to cancer treatment with Wnt inhibitors, in as far as mentioned in the claims.

25. claims: 29-31(completely); 32, 35-45(partially)

Wnt inhibitors for treatment of head and neck squamous cell carcinoma.

26. claims: 46-54

Uses of biomarkers from table 1, in as far as mentioned in the claims.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/059585

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JAMIE N. ANASTAS ET AL: "WNT signalling pathways as therapeutic targets in cancer", NATURE REVIEWS CANCER, vol. 13, no. 1, 21 December 2012 (2012-12-21), pages 11-26, XP055121831, ISSN: 1474-175X, DOI: 10.1038/nrc3419 supplementary table S2 -----	2,5-8, 11-19, 21-26, 32-45
X	K. D. PROFFITT ET AL: "Pharmacological Inhibition of the Wnt Acyltransferase PORCN Prevents Growth of WNT-Driven Mammary Cancer", CANCER RESEARCH, vol. 73, no. 2, 27 November 2012 (2012-11-27), pages 502-507, XP055121070, ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-12-2258 abstract -----	2,5-8, 11-19, 21-26, 32-45
X	SHIH-MIN A. HUANG ET AL: "Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling", NATURE, vol. 461, no. 7264, 16 September 2009 (2009-09-16), pages 614-620, XP055062115, ISSN: 0028-0836, DOI: 10.1038/nature08356 chapter "XAV939 inhibits growth of DLD-1 cancer cells" -----	2,5-9, 11-19, 21-26, 32-34, 38-45
X	E CLAPPIER ET AL: "NOTCH1 and FBXW7 mutations have a favorable impact on early response to treatment, but not on outcome, in children with T-cell acute lymphoblastic leukemia (T-ALL) treated on EORTC trials 58881 and 58951", LEUKEMIA, vol. 24, no. 12, 23 September 2010 (2010-09-23), pages 2023-2031, XP055122043, ISSN: 0887-6924, DOI: 10.1038/leu.2010.205 chapter "patients and methods"; abstract ----- -/--	1-8, 11-19, 21-28, 32-34, 38-45

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/059585

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>KRISTEN R GEORGIU ET AL: "Attenuated Wnt/ -catenin signalling mediates methotrexate chemotherapy-induced bone loss and marrow adiposity in rats", BONE, PERGAMON PRESS., OXFORD, GB, vol. 50, no. 6, 22 March 2012 (2012-03-22), pages 1223-1233, XP028423829, ISSN: 8756-3282, DOI: 10.1016/J.BONE.2012.03.027 [retrieved on 2012-03-29] abstract</p>	1
A	<p>FRED E. BERTRAND ET AL: "Developmental pathways in colon cancer: Crosstalk between WNT, BMP, Hedgehog and Notch", CELL CYCLE, vol. 11, no. 23, 1 December 2012 (2012-12-01), pages 4344-4351, XP055122055, ISSN: 1538-4101, DOI: 10.4161/cc.22134 the whole document</p>	1
T	<p>AN-MING WANG ET AL: "The autonomous notch signal pathway is activated by baicalin and baicalein but is suppressed by niclosamide in K562 cells", JOURNAL OF CELLULAR BIOCHEMISTRY, vol. 106, no. 4, 1 March 2009 (2009-03-01), pages 682-692, XP055122057, ISSN: 0730-2312, DOI: 10.1002/jcb.22065 the whole document</p>	
T	<p>YIMIN MA ET AL: "Inhibition of the Wnt-[beta]-catenin and Notch signaling pathways sensitizes osteosarcoma cells to chemotherapy", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 431, no. 2, 1 February 2013 (2013-02-01), pages 274-279, XP055121072, ISSN: 0006-291X, DOI: 10.1016/j.bbrc.2012.12.118</p>	
T	<p>J. LIU ET AL: "Targeting Wnt-driven cancer through the inhibition of Porcupine by LGK974", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 110, no. 50, 25 November 2013 (2013-11-25), pages 20224-20229, XP055121007, ISSN: 0027-8424, DOI: 10.1073/pnas.1314239110</p>	

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INTERNATIONAL SEARCH REPORT

International application No PCT/IB2014/059585

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	<p>N. J. WANG ET AL: "Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 108, no. 43, 17 October 2011 (2011-10-17), pages 17761-17766, XP055122110, ISSN: 0027-8424, DOI: 10.1073/pnas.1114669108</p> <p align="center">-----</p>	
T	<p>S. FRE ET AL: "Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, vol. 106, no. 15, 14 April 2009 (2009-04-14), pages 6309-6314, XP055122117, ISSN: 0027-8424, DOI: 10.1073/pnas.0900427106</p> <p align="center">-----</p>	