



- (51) **International Patent Classification:**
C07K 14/475 (2006.01) *C07K 14/705* (2006.01)
- (21) **International Application Number:**
PCT/EP2012/056950
- (22) **International Filing Date:**
16 April 2012 (16.04.2012)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
1106395.5 14 April 2011 (14.04.2011) GB
61/517,191 14 April 2011 (14.04.2011) 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, MD, 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).

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:**
20 December 2012

(54) **Title:** AGONISTS AND ANTAGONISTS OF THE WNT PATHWAY

(57) **Abstract:** The present invention relates to compounds that act as agonists of the Wnt signalling pathway, compositions comprising these compounds and the uses of these compounds, both therapeutic and in research. The invention also provides methods of identifying compounds that act as agonists of the Wnt signalling pathway.



INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2012/056950

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)

☐	on paper
☒	in electronic form
 - b. (time)

☒	in the international application as filed
☐	together with the international application in electronic form
☐	subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/056950

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K14/475 C07K14/705
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)

C07K

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, WPI Data, BIOSIS, EMBASE, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2005/072419 A2 (NUVELO INC [US]; KIRIN BREWERY [JP]; BOYLE BRYAN J [US]; FUNK WALTER []) 11 August 2005 (2005-08-11) abstract; sequence 91 -----	1-62,69, 70
X	EP 2 022 848 A1 (HUBRECHT INST [NL]) 11 February 2009 (2009-02-11) paragraph [0060]; claims 9-11,21 -----	1-62,69, 70
X	WO 2009/005809 A2 (ONCOMED PHARM INC [US]; GURNEY AUSTIN [US]) 8 January 2009 (2009-01-08) abstract; example 2 -----	1-70
X	WO 2010/016766 A2 (KONINK NL AKADEMIE VAN WETENSC [NL]; KONINK NL AKADEMIE VAN WETENSC [N]) 11 February 2010 (2010-02-11) abstract; example 10 ----- -/-	1-62,69, 70



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 November 2012

Date of mailing of the international search report

15/11/2012

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/056950

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/208484 A1 (CHRISTIANO ANGELA M [US]) 20 August 2009 (2009-08-20) abstract; sequence 103 -----	1-62, 69, 70
X	NAM JU-SUK ET AL: "Mouse cristin/R-spondin family proteins are novel ligands for the frizzled 8 and LRP6 receptors and activate beta-catenin-dependent gene expression", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 281, no. 19, May 2006 (2006-05), pages 13247-13257, XP002679925, ISSN: 0021-9258 figures 1c, 3b, 7c -----	1-62, 69, 70
X, P	DE LAU WIM ET AL: "Lgr5 homologues associate with Wnt receptors and mediate R-spondin signalling", NATURE (LONDON), vol. 476, no. 7360, August 2011 (2011-08), pages 293 URL-HTTP://WW, XP002679926, abstract -----	1-62, 69, 70
X	SASAKI YUKA ET AL: "Establishment of a novel monoclonal antibody against LGR5", BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 394, no. 3, April 2010 (2010-04), pages 498-502, XP002685669, abstract -----	63-68
A	YAMAMOTO Y ET AL: "OVEREXPRESSION OF ORPHAN G-PROTEIN-COUPLED RECEPTOR, GPR49, IN HUMAN HEPATOCELLULAR CARCINOMAS WITH BETA-CATENIN MUTATIONS", HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 37, no. 3, 1 March 2003 (2003-03-01), pages 528-533, XP008041122, ISSN: 0270-9139, DOI: 10.1053/JHEP.2003.50029 abstract -----	63-68
A	XIANG-SHAN FAN ET AL: "Expression of Lgr5 in human colorectal carcinogenesis and its potential correlation with I-catenin", INTERNATIONAL JOURNAL OF COLORECTAL DISEASE ; CLINICAL AND MOLECULAR GASTROENTEROLOGY AND SURGERY, SPRINGER, BERLIN, DE, vol. 25, no. 5, 27 February 2010 (2010-02-27), pages 583-590, XP019802019, ISSN: 1432-1262 abstract -----	63-68
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/056950

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CARMON KENDRA S ET AL: "LGR5 Interacts and Cointernalizes with Wnt Receptors To Modulate Wnt/beta-Catenin Signaling", MOLECULAR AND CELLULAR BIOLOGY, vol. 32, no. 11, 2 April 2012 (2012-04-02), pages 2054-2064, XP009163870, abstract -----	1-70

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/056950

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005072419	A2	11-08-2005	
		AU 2005208945 A1	11-08-2005
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		US 2009208484 A1	20-08-2009
		WO 2008020942 A2	21-02-2008

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2012/056950

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.:

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: 1-62, 69, 70

relate to an agonist of the Wnt pathway which binds to an Lgr protein and mimics the activity of an Rspodin protein; the corresponding methods and uses.

1.1. claims: 23, 24, 34-36, 58(completely); 1-22, 26-29, 31-33, 38-49, 51-56, 59-62, 69, 70(partially)

relate to an agonist of the Wnt pathway comprising a fragment or derivative of Rspodin which binds to an Lgr protein and mimics the activity of an Rspodin protein; the corresponding methods and uses.

1.2. claims: 25, 30, 37, 50, 57(completely); 1-22, 26-29, 31-33, 38-49, 51-56, 59-62, 69, 70(partially)

relate to an agonist of the Wnt pathway comprising an antibody or antibody fragment which binds to an Lgr protein and mimics the activity of an Rspodin protein; the corresponding methods and uses.

2. claims: 63-68

relate to a bispecific compound which binds to both Lgr4 and Lgr5 and inhibits beta-catenin signalling and the corresponding compositions and uses.
