

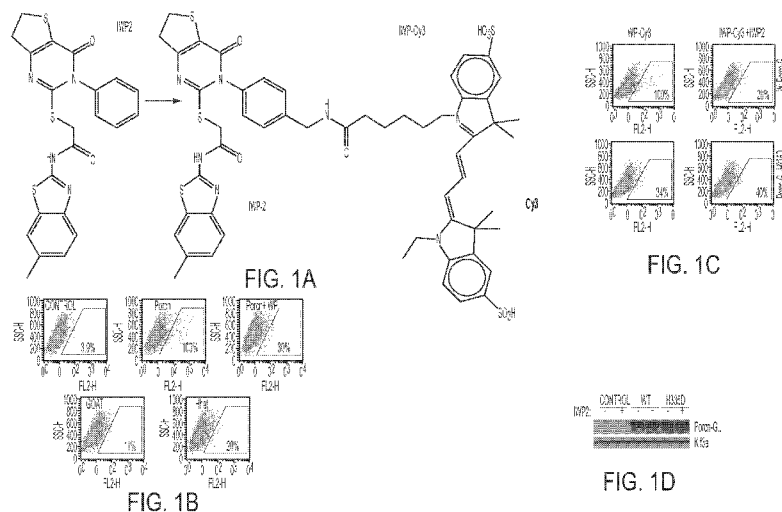


- (51) **International Patent Classification:**
A61K 31/44 (2006.01)
- (21) **International Application Number:**
PCT/US2013/039655
- (22) **International Filing Date:**
6 May 2013 (06.05.2013)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/645,924 11 May 2012 (11.05.2012) 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, 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, 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, PA, 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).

Published:

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

[Continued on next page]

(54) **Title:** WNT PROTEIN SIGNALLING INHIBITORS

(57) **Abstract:** The present invention generally relates to protein signalling. In particular, compounds that inhibit the Wnt protein signalling pathway are disclosed. Such compounds may be used in the treatment of Wnt protein signalling-related diseases and conditions such as cancer, degenerative diseases, type II diabetes and osteopetrosis.



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- *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:**
9 January 2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/039655

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/44 (2013.01)

USPC - 514/344

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)

IPC(8) - A61K 31/44 (2013.01)

USPC - 514/344, 345

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
CPC - A61K 31/44 (2013.01)

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

PatBase, Orbit, STN, PubChem, Google Scholar

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,135,486 B1 (ROSENTERER et al) 14 November 2006 (14.11.2006) entire document	18-20, 52-54, 69-71
Y	DYACHENKO et al. Synthesis of 4-alkyl-6-amino-3,5-dicyano-2(1H)-pyridinethiones. Chemistry of Heterocyclic Compounds 33(12): 1430-1437, 1997. entire document	18-20, 52-54, 69-71
A	US 2011/0136813 A1 (LUM et al) 09 June 2011 (09.06.2011) entire document	1-3, 18-20, 35-37, 52-54, 69-71
A	US 7,504,421 B2 (ROSENTERER et al) 17 March 2009 (17.03.2009) entire document	1-3, 18-20, 35-37, 52-54, 69-71
A	WO 2010/139966 A1 (HOLSWORTH et al) 09 December 2010 (09.12.2010) entire document	1-3, 18-20, 35-37, 52-54, 69-71
A	US 2012/0100609 A1 (CRAWFORD et al) 26 April 2012 (26.04.2012) entire document	1-3, 18-20, 35-37, 52-54, 69-71
X, P	DODGE et al. Diverse Chemical Scaffolds Support Direct Inhibition of the Membrane-bound O-Acyltransferase Porcupine. The Journal of Biological Chemistry, 287(27): 23246-23254, June 29, 2012. entire document	1-3, 18-20, 35-37, 52-54, 69-71

☐ Further documents are listed in the continuation of Box C.


* 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

"G" document member of the same patent family

Date of the actual completion of the international search

06 November 2013

Date of mailing of the international search report

14 NOV 2013

Name and mailing address of the ISA/US

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P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

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PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2013/039655

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 Extra Sheets

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.:
1-3, 18-20, 35-37, 52-54, 69-71

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.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-80 are drawn to methods of inhibiting Wnt protein signaling in a cell, treating cancer in a subject, treating or preventing osteopetrosis in a patient, and treating a degenerative disease in a patient, said methods comprising administering to the cell or to the patient an effective amount of a compound of formula II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII; and a pharmaceutical composition comprising an effective amount of a compound of formula II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII.

The first invention of Group I+ is restricted to a method or pharmaceutical composition comprising a compound selected to be 2-amino-6-([2-oxo-2-(4-phenylphenyl)ethyl]sulfanyl)-4-(propan-2-yl)pyridine-3,5-dicarbonitrile of formula II. It is believed that claims 1-3, 18-20, 35-37, 52-54, and 69-71 read on this first named invention and thus these claims will be searched without fee to the extent that they read on 2-amino-6-([2-oxo-2-(4-phenylphenyl)ethyl]sulfanyl)-4-(propan-2-yl)pyridine-3,5-dicarbonitrile of formula II.

Applicant is invited to elect additional formula(e) for each additional formula to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a pharmaceutical composition or method comprising a compound selected to be 2-amino-4-(2-methylpropyl)-6-([2-oxo-2-(4-phenylphenyl)ethyl]sulfanyl)pyridine-3,5-dicarbonitrile of formula II. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ 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 Groups I+ formulae do not share a significant structural element, requiring the selection of alternatives for the compound responsible for inhibiting a Wnt protein, treating cancer, treating or preventing osteopetrosis, or treating a degenerative disease comprising administering "a compound of the formula: II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII."

The Groups I+ share the technical features of a method of inhibiting Wnt protein signaling in a cell, a method of treating cancer in a subject, a method of treating or preventing osteopetrosis in a patient, and a method of treating a degenerative disease in a patient, comprising administering to the cell or to the patient an effective amount of a compound of formula II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII; and a pharmaceutical composition comprising an effective amount of a compound of formula II, III, IV, V, VI, VII, VIII, IX, X, XI, or XII. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 2011/0136813 A1 to Lum et al. discloses a method of inhibiting Wnt protein signaling in a cell (the invention provides a method of inhibiting Wnt protein signalling in a cell, Para. [0035]; method of inhibiting Wnt protein signaling is further defined as a method of inhibiting Wnt response. In some embodiments, the method further comprises one of the specific compounds described, Para. [0040]), a method of treating cancer in a subject (specific compounds described herein are also contemplated in methods of treating cancer, Para. [0041]), a method of treating or preventing osteopetrosis in a patient (the present invention contemplates a method of treating or preventing osteopetrosis in a patient comprising administering to the patient an effective amount of a compound disclosed herein, Para. [0045]), and a method of treating a degenerative disease in a patient (the present invention are methods of treating a degenerative disease in a patient comprising administering to the patient an effective amount of a compound disclosed herein, Para. [0046]), comprising administering to the cell or to the patient an effective amount of a compound (the invention provides a method of inhibiting Wnt protein signalling in a cell comprising administering to the cell an effective amount of a compound, Para. [0035]) of formula X (the present invention provides a method of inhibiting Wnt protein signaling in a cell comprising administering to the cell an effective amount of a compound of formula (A) (where formula A of Lum et al. is formula X of the instant application, where for formula A, R1 is N-(1,3-benzothiazol-2-yl)-2-((4-oxo-3H,4H,6H,7H-thieno[3,2-d]pyrimidin-2-yl)sulfanyl)acetamide, R11 is methyl, and R2 and R3 are each hydrogen)); and a pharmaceutical composition comprising an effective amount of a compound of formula X (the compounds disclosed herein may be combined with a pharmaceutically acceptable carrier, diluent, and/or excipient in a pharmaceutical composition, Para. [0043]; of a compound of formula (A) (where formula A of Lum et al. is formula X of the instant application, where for formula A, R1 is N-(1,3-benzothiazol-2-yl)-2-((4-oxo-3H,4H,6H,7H-thieno[3,2-d]pyrimidin-2-yl)sulfanyl)acetamide, R11 is methyl, and R2 and R3 are each hydrogen)).

Additionally, Lum et al. discloses a compound of the shared core structure of formula XI of the instant application (In certain embodiments, the compound of formula (I) is further defined as a compound of formula (IV) (where formula IV of Lum et al. represents the core structure of formula XI of the instant application when R31 is 2-((4-oxo-3-phenyl-3H,4H,6H,7H-thieno[3,2-d]pyrimidin-2-yl)sulfanyl)-N-phenylacetamide, R34 and R35 are each hydrogen, R32 is quinoline, and R36 is hydrogen)). As said compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula XI.

Further, US 7,504,421 B2 to Rosentreter et al. discloses a compound of the shared core structure of formula II of the instant application (administering the compounds of the general formula (I), Col. 20, Lns. 15-16; compound A8, Col. 53). As said compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula II.

Additionally, WO 2010/139966 A1 to Holsworth et al. discloses a compound of the shared core structure of formula IV of the instant application (said method comprising the step of administering to said body an effective amount of a compound of formula I, II, Ia, IIa, Ib, IIb, Ic, IIc, IId or IIe as herein defined or a pharmaceutically acceptable salt thereof, Pg. 57, second full paragraph; compound 92, Pg. 34). As said compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula IV.

Moreover, US 2012/0100609 A1 to Crawford et al. discloses a compound of the shared core structure of formula V of the instant application (provided herein are N-linked glycan inhibitors, Abstract; selective N-linked glycan biosynthesis inhibitors according to certain embodiments, Para. [0087] and figs. 31A-T; N-(4-chloro-2-methoxy-5-methylphenyl)-2-((4-methyl-6-oxo-6H-benzo[c]chromen-3-yl)oxy) acetamide, fig. 31K, third column, fourth down). As said compound was known in the art at the time of invention, this cannot be considered a special technical feature that would otherwise unify the compounds sharing the core structure of formula V.

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.