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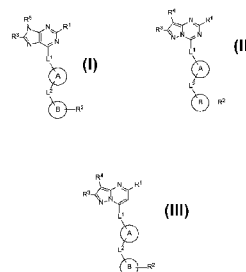
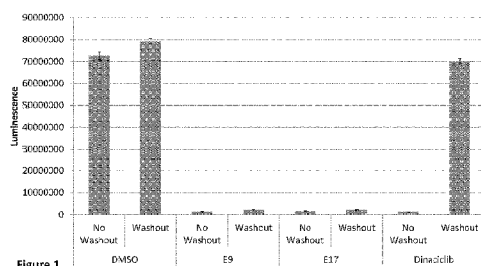
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Published:

- 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))

- (88) Date of publication of the international search report:
17 November 2016

(54) Title: INHIBITORS OF CYCLIN-DEPENDENT KINASES



(57) Abstract: The present invention provides novel compounds of Formula (I), (II), or (III), and pharmaceutically acceptable salts, solvates, hydrates, polymorphs, co-crystals, tautomers, stereoisomers, isotopically labeled derivatives, prodrugs, and compositions thereof. Also provided are methods and kits involving the inventive compounds or compositions for treating and/or preventing proliferative diseases (e.g., cancers (e.g., leukemia, acute lymphoblastic leukemia, lymphoma, Burkitt's lymphoma, melanoma, multiple myeloma, breast cancer, Ewing's sarcoma, osteosarcoma, brain cancer, ovarian cancer, neuroblastoma, lung cancer, colorectal cancer), benign neoplasms, diseases associated with angiogenesis, inflammatory diseases, autoimmune diseases, and autoimmune diseases) in a subject. Treatment of a subject with a proliferative disease using a compound or composition of the invention may inhibit the aberrant activity of a kinase, such as a cyclin-dependent kinase (CDK) (e.g., CDK7, CDK12, or CDK13), and therefore, induce cellular apoptosis and/or inhibit transcription in the subject.

WO 2016/160617 A3

INTERNATIONAL SEARCH REPORT

International application No.

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Box No. 1 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, the international search was carried out on the basis of a sequence listing:
 - a. forming part of the international application as filed:
 - in the form of an Annex C/ST.25 text file.
 - on paper or in the form of an image file.
 - b. furnished together with the international application under PCT Rule 13ter. 1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. furnished subsequent to the international filing date for the purposes of international search only:
 - in the form of an Annex C/ST.25 text file (Rule 13ter. 1(a)).
 - on paper or in the form of an image file (Rule 13ter. 1(b) and Administrative Instructions, Section 713).
2. In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of 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.

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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.: 8-41, 100, 104-161
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 attached extra 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 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.:
1,4-7(in part), 42-60,103

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

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A. CLASSIFICATION OF SUBJECT MATTER IPC(8) - A61K 31/535 (2016.01) CPC - C07D 401/12; C07D 471/04; C07D 401/04 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 31/535 (2016.01) CPC: C07D 401/12; C07D 471/04; C07D 401/04 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched USPC: 514/228.2,228.5 Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) PatBase; Keyword limited: Kinase; Cyclin dependent/Cyclin-dependent kinase; inhibit; treating/preventing proliferative diseases/cancers/leukemia/lymphoma/melanoma/inflammatory/autoinflammatory/autoimmune diseases		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2008/0090849 A1 (BORDON-PALLIER et al.) 17 April 2008 (17.04.2008), entire document, especially: abstract; para [0236]-[0239], Example 7, Trans-N2-(4-aminocyclohexyl)-N6-[1-(phenylmethyl)-4-piperidinyl]-1H-purine-2, 6-diamine trihydrochloride; para [0253]-[0255], Example 12, Trans-N2-(4-aminocyclohexyl)-N6-(4-fluorophenylmethyl)-1H-purine-2,6-diamine; para [0262]-[0263], Example 16, trans-N2-(4-aminocyclohexyl)-N6-(3,4-dichlorophenyl)-9H-purine-2,6-diamine	1, 4, 6-7,42-47 ----- 5, 48-60
X	U3 2012/0094999 A1 (GRAY et al.) 19 April 2012 (19.04.2012), entire document, especially: Table 1, pg 23, Compound number 1-15	103
Y	US 2014/0303112 A1 (CHEN et al.) 9 October 2014 (09.10.2014), entire document, especially: abstract; para [0056], Example 6, 2-methyl-6-(3-chlorobenzylamino)purine; para [0058], Table 4, row 10, cyclohexylamino substituent for R6	5,48-49
Y	ODINGO et al. "Synthesis and evaluation of the 2,4-diaminoquinazoline series as anti-tubercular agents", Bioorganic & Medicinal Chemistry. 2014. Vol 22, pp 6965-6979, entire document, especially: pg 6966, Table 1, Compound 61; pg 6967, col 2, Table 2, Compound 74; pg 6977, col 2, 4.6.3.13, N-(4-Fluorobenzyl)-2-(piperidin-1-yl) 9H-purin-6-amine (74)	50-60
A	PubChem-CID-68365059, create date: 30 November 2012, page 3 formula	1,4-7,42-60,103
<input type="checkbox"/> 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 "&" document member of the same patent family
Date of the actual completion of the international search 22 September 2016 (22.09.2016)		Date of mailing of the international search report 06 OCT 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300		Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

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lack of unity

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.

Group I: Claims 1, 4-7 (in part), 42-60, 103 (in part) directed to a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

Group II: Claims 2, 4-7 (in part), 61-78, 103 (in part) directed to a compound of Formula (II), or a pharmaceutically acceptable salt thereof.

Group III: Claims 3, 4-7 (in part), 79-102, 103 (in part) directed to a compound of Formula (III), or a pharmaceutically acceptable salt thereof.

The groups of inventions listed above 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:

Special Technical Features:

Group I includes the technical feature of a unique compound of Formula (I), which is not required by any other invention of Groups II-III.

Group II includes the technical feature of a unique compound of Formula (II), which is not required by Groups I and III.

Group III includes the technical feature of a unique compound of Formula (III), which is not required by Groups I-II.

Common technical features:

The inventions of Groups I-III share the technical feature of 5-membered heteroaryl fused to a 6-membered heteroaryl ring wherein there is a nitrogen atom adjacent to one of the bridging atoms in the 6-membered ring and the opposite position of the 6-membered ring is substituted with -L1-A-L2-B-R2. This invention does not represent a contribution over prior art, as being anticipated by the document PubChem-CID-68365059 ('PubChem-059'). PubChem-059 teaches a compound wherein pyrazolo[4,3-d]pyrimidine is substituted at the 7 position with L1 wherein L1 is -NRL1-(CH2)t-; RL1 is hydrogen; t is 2; Ring A is unsubstituted aryl; L2 is NRL2; RL2 is hydrogen; Ring B is unsubstituted heteroaryl; and R2 is Formula (i-36), which is -L3-C1 wherein L3 is a bond (pg 3, Fig).

As said compound was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the inventions of Group I-III.

The inventions of Groups I, II and III thus lack unity under PCT Rule 13.

Note reg. item 4: Claims 8-41, 100 and 104-161 are unsearchable because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a). These claims are therefore not included in the above analysis.