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(71) Applicant: **THE UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECRETARY, DEPARTMENT OF HEALTH & HUMAN SERVICES** [US/US]; Office Of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852 (US).

(72) Inventors: **QIAN, Wenjian**; 1050 Boyles Street, Building 376 -fcrdc, 217, Frederick, MD (US). **PARK, Jung, Eun**; 1050 Boyles Street, Building 376 -fcrdc, 217, North Bethesda, MD (US). **LAI, Christopher, C.**; 7523 Talbots Woods Court, Ellicott City, MD 21043 (US). **KELLEY, James, A.**; 13009 Valleywood Drive, Silver Spring, MD 20906 (US). **LEE, Kyung, S.**; 12616 Carrington Hill Drive, Gaithersburg, MD 20878 (US). **BURKE, Terrence, R.**; No. 410, Bethesda, MD 20817 (US).

(74) Agents: **CORLESS, Peter, F.** et al.; Edwards Wildman Palmer LLP, P.O. Box 55874, Boston, MA 02205 (US).

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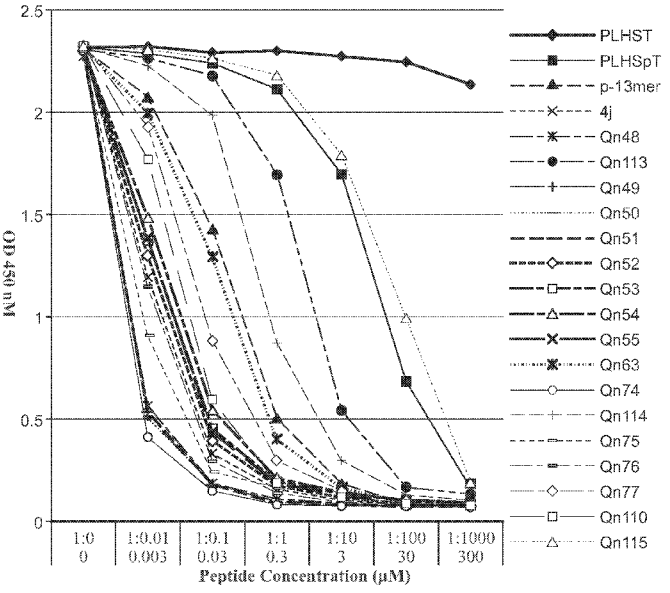
[Continued on next page]

(54) Title: PEPTIDE AND PEPTIDE MIMETIC BINDING ANTAGONISTS OF POLO-LIKE KINASE 1 POLO BOX DOMAIN AND METHODS OF USE

FIG. 1



(57) Abstract: The invention provides novel compounds that may serve as anticancer therapeutics. The compounds of the invention bind to polo-like kinases through the polo-box domain. In certain embodiments, the compounds of the invention are POM-protected peptide derivatives. The use of cationic bis-alkyl his residues in combination with a mono POM-protected phophoryl group results in a peptide possessing an overall neutral charge. The peptide derivatives of the invention have achieved both good efficacy and an enhanced bioavailability. The invention also provides methods of use, compositions, and kits thereof. Further, the invention provides a novel method of design and/or synthesis of phosphoryl-derived peptide derivatives useful as therapeutic agents.

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Declarations under Rule 4.17:

— *as to non-prejudicial disclosures or exceptions to lack of novelty (Rule 4.17(v))*

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:
8 January 2015

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/029071

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K7/06 A61K38/08 C12N9/12
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 A61K C12N

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, 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	WO 2012/142245 A2 (US GOV HEALTH & HUMAN SERV [US]; BURKE TERRENCE R [US]; QIAN WENJIAN [) 18 October 2012 (2012-10-18) cited in the application	1-7,10, 11,13, 15-17, 21-28
A	p. 28, last paragraph - p. 112, last paragraph, comp. 4j, 4j-A, 3j, 3j-A, cl. 1-83	8,9,12, 14,18-20

X	US 2012/065146 A1 (BURKE JR TERRENCE R [US] ET AL) 15 March 2012 (2012-03-15) cited in the application	1-7,10, 11,13, 15-17, 21-28
A	p. 1, paragraph [0005] - p. 14, paragraph [0097], p. 41, paragraph [0266] - p. 47, paragraph [0287], p. 70, paragraph [0312] - p. 95, paragraph [0337], Table 11, comp. 5	8,9,12, 14,18-20

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
8 July 2014	17/11/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	R. von Eggelkraut-G.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2014/029071

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.:

1-28

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

International application No
PCT/US2014/029071

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FA LIU ET AL: "Serendipitous alkylation of a Plk1 ligand uncovers a new binding channel", NATURE CHEMICAL BIOLOGY, vol. 7, no. 9, 1 January 2011 (2011-01-01) , pages 595-601, XP055032617, ISSN: 1552-4450, DOI: 10.1038/nchembio.614 the whole document	1-28
A	QIAN WENJIAN ET AL: "Effects on polo-like kinase 1 polo-box domain binding affinities of peptides incurred by structural variation at the phosphoamino acid position", BIOORGANIC & MEDICINAL CHEMISTRY, vol. 21, no. 14, 26 May 2012 (2012-05-26), pages 3996-4003, XP028595028, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2012.05.036 the whole document	1-28
A	LIU F ET AL: "Preparation of orthogonally protected (2S,3R)-2-amino-3-methyl-4-phosphonobutyric acid (Pmab) as a phosphatase-stable phosphothreonine mimetic and its use in the synthesis of polo-box domain-binding peptides", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 65, no. 47, 21 November 2009 (2009-11-21), pages 9673-9679, XP026696877, ISSN: 0040-4020, DOI: 10.1016/J.TET.2009.09.093 [retrieved on 2009-09-26] the whole document	1-28
X,P	WEN-JIAN QIAN ET AL: "Peptide-Based Inhibitors of Plk1 Polo-box Domain Containing Mono-anionic Phosphothreonine Esters and Their Pivaloyloxymethyl Prodrugs", CHEMISTRY & BIOLOGY, vol. 20, no. 10, 1 October 2013 (2013-10-01), pages 1255-1264, XP055126907, ISSN: 1074-5521, DOI: 10.1016/j.chembiol.2013.09.005 the whole document	1-28

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/029071

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	WEN-JIAN QIAN ET AL: "Design and synthesis of a reagent for solid-phase incorporation of the phosphothreonine mimetic (2S,3R)-2-amino-3-methyl-4-phosphonobutyric acid (Pmab) into peptides in a bio-reversible phosphonyl-bis-pivaloyloxymethyl (POM) prodrug form", AMINO ACIDS, vol. 45, no. 5, 1 November 2013 (2013-11-01), pages 1143-1148, XP055126918, ISSN: 0939-4451, DOI: 10.1007/s00726-013-1567-0 the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/029071

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012142245 A2	18-10-2012	AU 2012242784 A1	31-10-2013
		CA 2832073 A1	18-10-2012
		EP 2686342 A2	22-01-2014
		JP 2014511877 A	19-05-2014
		US 2014142044 A1	22-05-2014
		WO 2012142245 A2	18-10-2012
US 2012065146 A1	15-03-2012	US 2012065146 A1	15-03-2012
		WO 2010132869 A2	18-11-2010

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-28

   5-mer peptide compounds as disclosed in claims 1-20 and their use in the treatment of hyperproliferative disorders and in a chemical library

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2. claims: 29-34

   POM-protected amino acid analogues as disclosed in claims 29 and 30 and their use in peptide synthesis

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