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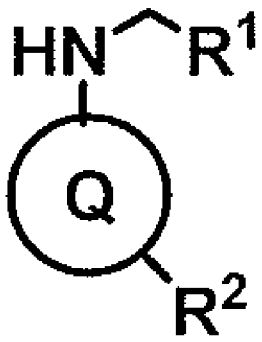
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR,

[Continued on next page]

(54) Title: INHIBITORS OF THE USP1/UAF1 DEUBIQUITINASE COMPLEX AND USES THEREOF



(I)

(57) Abstract: Disclosed are inhibitors of the USP1/UAF1 deubiquitinase complex, for example. of formula (I), wherein R^1, R^2, and Q are as defined herein, which are useful in treating diseases such as cancer, and improving the efficacy of DNA damaging agents in cancer treatment. Also disclosed is a composition comprising a pharmaceutically suitable carrier and at least one compound of the invention, a method of method of inhibiting a heterodimeric deubiquitinase complex in a cell, and a method of enhancing the chemotherapeutic treatment of cancer in a mammal undergoing treatment with an anti cancer agent. Further disclosed is a method of preparing compounds of the invention.

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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.

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A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/12 C07D239/94 C07D473/00 C07D487/02 C07D491/048
A61K31/517 A61K31/519 A61K31/52 A61K31/53
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)
C07D

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, CHEM ABS 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 2008/040753 A1 (NEUROSEARCH AS [DK]; ERIKSEN BIRGITTE L [DK]; SOERENSEN ULRIK SVANE [D) 10 April 2008 (2008-04-10) Sixth and seventh compounds in claim 8; claim 11	1-7,9, 11,14, 20-30
X,P	WO 2013/004332 A1 (MERCK PATENT GMBH [DE]; HEINRICH TIMO [DE]; BRUGGER NADIA [US]; JOSEPH) 10 January 2013 (2013-01-10) claims 5-14; compounds 89,93,139-142,210	1-8, 20-30
X	WO 2005/103022 A1 (TRANSTECH PHARMA INC [US]; MJALLI ADNAN M M [US]; GADDAM BAPU R [US];) 3 November 2005 (2005-11-03) claims 23,33; examples 149-151,153,155,157	1-3,5-8, 11,20-30

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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)

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"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
24 February 2014	22/07/2014

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	Cooper, Simon

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/077804

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	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; SATO, JUNJI ET AL: "2-(Pyridin-2-yl)pyrimidin-4-amine compound and salt thereof, and their use for pharmaceutical composition for treatment of diseases related to RANKL/RANK signals", XP002720347, retrieved from STN Database accession no. 2013:516354 All individual compounds apart from the first one. & WO 2013/047719 A1 (ASTELLAS PHARMA INC., JAPAN; WAKUNAGA PHARMACEUTICAL CO., LTD.) 4 April 2013 (2013-04-04) -----	1-7,12, 20,30
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FUJIWARA, HIDEYASU ET AL: "Preparation of 4-aminopyrimidine derivatives as IKK2 inhibitors", XP002720348, retrieved from STN Database accession no. 2011:199450 abstract & JP 2011 032169 A (GENECARE RESEARCH INSTITUTE CO., LTD., JAPAN) 17 February 2011 (2011-02-17) -----	1-8,11, 20,30
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KOKUBO, SHIGERU ET AL: "Preparation of heterocyclic compounds as CCR4 or TARC and/or MDC function regulators", XP002720349, retrieved from STN Database accession no. 2010:1193251 12th,14th and 16th individual compound & JP 2010 208945 A (TANABE SEIYAKU CO., LTD., JAPAN) 24 September 2010 (2010-09-24) -----	1-7,20, 30
X	DATABASE CAPLUS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YONETOKU, YASUHIRO ET AL: "Preparation of 4-aminopyrimidine derivatives as insulin secretion accelerators", XP002720350, retrieved from STN Database accession no. 2003:261678 abstract -/--	1-8,11, 20,30

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& WO 03/026661 A1 (YAMANOUCHI PHARMACEUTICAL CO., LTD., JAPAN) 3 April 2003 (2003-04-03)	
X,P	COOMBS THOMAS C ET AL: "Small-molecule pyrimidine inhibitors of the cdc2-like (Clk) and dual specificity tyrosine phosphorylation-regulated (Dyrk) kinases: Development of chemical probe ML315", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 23, no. 12, 30 March 2013 (2013-03-30), pages 3654-3661, XP028543373, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2013.02.096 Scheme 1; table 2; compounds 30-32	1-8,11, 20
X	SUH, B.C. ET AL: "SYNTHESIS AND BIOLOGICAL EXAMINATION OF NEW PYRIMIDINE TYPE DERIVATIVES AS POTENTIAL PHOSPHODIESTERASE(PDE) INHIBITORS", CHEMINFORM, vol. 29, no. 47, 24 November 1998 (1998-11-24), XP002720351, compounds VIa-c	1-7,12
X	MA Y ET AL: "COMBINATORIAL SYNTHESIS OF SUBSTITUTED BIARYLS AND HETEROCYCLIC ARYLAMINES", JOURNAL OF COMBINATORIAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 6, no. 3, 4 January 2004 (2004-01-04) , pages 426-430, XP009064582, ISSN: 1520-4766, DOI: 10.1021/CC0340731 Entries 10e and 10g in table 2.	1-7
X	TAREK MOHAMED ET AL: "Design, synthesis and structure-activity relationship (SAR) studies of 2,4-disubstituted pyrimidine derivatives: Dual activity as cholinesterase and A-aggregation inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY, PERGAMON, GB, vol. 19, no. 7, 16 February 2011 (2011-02-16), pages 2269-2281, XP028157411, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2011.02.030 [retrieved on 2011-03-01] table 1; compounds 7a-c,u;9a-c	1-7,11, 20

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JUNJI MIYATA ET AL: "Orally available pyridinylpyrimidine derivatives as novel RANKL-induced osteoclastogenesis inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 22, no. 17, 6 July 2012 (2012-07-06), pages 5681-5684, XP055064704, ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2012.06.087 tables 2,3; compounds 15,17-23	1-7,12, 20,30
X	DING ET AL: "A Combinatorial Scaffold Approach toward Kinase-Directed Heterocycle Libraries", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, ACS PUBLICATIONS, US, vol. 124, no. 8, 2 February 2002 (2002-02-02), pages 1594-1596, XP002210160, ISSN: 0002-7863, DOI: 10.1021/JA0170302 Entries 1-3 in table 2 in respect of Y1	1-7
X	WO 2011/026835 A1 (VIFOR INT AG [CH]; DUERRENBERGER FRANZ [CH]; BURCKHARDT SUSANNA [CH];) 10 March 2011 (2011-03-10) claim 14; examples 20,24	1-7,11, 20,30
X	EP 1 254 903 A1 (CIBA SC HOLDING AG [CH]) 6 November 2002 (2002-11-06) claim 26; compounds 88,91,97	1-7,11, 20
X	EP 2 360 158 A1 (ALMIRALL SA [ES]) 24 August 2011 (2011-08-24) claims 19,20,25; example 22	1-7,11, 20-30
X	WO 03/077656 A1 (CIBA SC HOLDING AG [CH]; MARQUAIS-BIENEWALD SOPHIE [FR]; HOELZL WERNER) 25 September 2003 (2003-09-25) compounds 45,49,51	1-7,11
A	JUNJUN CHEN ET AL: "Selective and Cell-Active Inhibitors of the USP1/UAF1 Deubiquitinase Complex Reverse Cisplatin Resistance in Non-small Cell Lung Cancer Cells", CHEMISTRY & BIOLOGY, vol. 18, 22 November 2011 (2011-11-22), pages 1390-1400, XP002720352, the whole document	1-9,11, 12,14, 15,18, 20-30

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/077804

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.:

see annexe

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: 3, 7, 18, 30(completely); 1, 2, 4-6, 8, 9, 11, 12, 14, 15, 20-29(partially)

   Compounds according to claim 2 in which Q has the first definition, their uses and synthesis and pharmaceutical compositions comprising them

   ---

2. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the second definition, their uses and pharmaceutical compositions comprising them

   ---

3. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the third definition, their uses and pharmaceutical compositions comprising them

   ---

4. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the fourth definition, their uses and pharmaceutical compositions comprising them

   ---

5. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the fifth definition, their uses and pharmaceutical compositions comprising them

   ---

6. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the sixth definition, their uses and pharmaceutical compositions comprising them

   ---

7. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

   Compounds according to claim 2 in which Q has the seventh definition, their uses and pharmaceutical compositions comprising them

   ---

8. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

Compounds according to claim 2 in which Q has the eighth definition, their uses and pharmaceutical compositions comprising them

---

9. claims: 1, 2, 4-6, 8, 9, 11-15, 19-29(all partially)

Compounds according to claim 2 in which Q has the ninth definition, their uses and pharmaceutical compositions comprising them

---

10. claims: 10, 16, 17(completely); 1, 2, 4-6, 8, 9, 11, 12, 14, 15, 20-29(partially)

Compounds according to claim 2 in which Q has the tenth definition, their uses and pharmaceutical compositions comprising them

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2013/077804

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