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6 September 2013

(54) Title: COMPOUNDS & METHODS FOR THE ENHANCED DEGRADATION OF TARGETED PROTEINS & OTHER POLYPEPTIDES BY AN E3 UBIQUITIN LIGASE

(57) Abstract: The present invention relates to bifunctional compounds, which find utility as modulators of targeted ubiquitination, especially inhibitors of a variety of polypeptides and other proteins which are degraded and/or otherwise inhibited by bifunctional compounds according to the present invention. In particular, the present invention is directed to compounds, which contain on one end a VHL ligand which binds to the ubiquitin ligase and on the other end a moiety which binds a target protein such that the target protein is placed in proximity to the ubiquitin ligase to effect degradation (and inhibition) of that protein. The present invention exhibits a broad range of pharmacological activities associated with compounds according to the present invention, consistent with the degradation/inhibition of targeted polypeptides.



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A. CLASSIFICATION OF SUBJECT MATTER**C07K 19/00(2006.01)i, C07D 413/12(2006.01)i, C07D 413/14(2006.01)i, C07D 207/26(2006.01)i, C07J 9/00(2006.01)i, C1**

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 19/00; A61K 38/43; C12Q 1/00; C12N 5/02; C12Q 1/48; C07K 1/00; A61K 38/12; A61K 31/535; C07K 14/00; A61K 38/16; C12N 15/00; C40B 30/04; C07D 413/12; C07D 413/14; C07D 207/26; C07J 9/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: ubiquitin ligase, degrade, inhibit, target protein ,
bifunctional compound, E3 ligase, Von Hippel Lindau, VHL, transcription gactor HIF-1α**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-008260 A2 (PRESIDENT AND FELLOWS OF HARVARD COLLEGE) 20 January 2011 See claims 1, 46 and 91; paragraphs [0009], [0013], [0023], [0078]-[0082], [0137] and [0294].	1,2
A		3,4,39(2),40(2), 42-45,55-90,102
A	AGHAJANY, MARIAM et al., 'Chemical genetics screen for enhancers of rapamycin identifies a specific inhibitor of an SCF family E3 ubiquitin ligase', Nature Biotechnology, 27 June 2010, Vol. 28, No. 7, pp. 738-742. See the whole document.	1-4,39(2),40(2), 42-45,55-90,102
A	WO 00-50445 A1 (OKLAHOMA MEDICAL RESEARCH FOUNDATION) 31 August 2000 See claims 8-9; p. 15.	1-4,39(2),40(2), 42-45,55-90,102
A	WO 2010-107485 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 23 September 2010 See claims 1, 13-17 and 30-31; paragraph [0265].	1-4,39(2),40(2), 42-45,55-90,102
A	WO 2012-003281 A2 (BRANDEIS UNIVERSITY) 5 January 2012 See claims 1-4; p 21-22.	1-4,39(2),40(2), 42-45,55-90,102



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 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

26 June 2013 (26.06.2013)

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/021136

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00-22110 A1 (PRESEIDENT AND FELLOWS OF HARVARD COLLEGE) 20 April 2000 See claims 1-4; pp. 11-12 and 21.	1-4,39(2),40(2) ,42-45,55-90,102
A	WO 01-75145 A2 (RIGEL PHARMACEUTICALS, INC.) 11 October 2001 See claim 104.	1-4,39(2),40(2) ,42-45,55-90,102
A	WO 2011-160016 A2 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 22 December 2011 See claims 1 and 4.	1-4,39(2),40(2) ,42-45,55-90,102
PX	BUCKLEY, DENNIS L. et al., `Targeting the von Hippel-Lindau E3 ubiquitin ligase using small molecules to disrupt the VHL/HIF-1 $\alpha$ interaction`, Journal of The American Chemical Society, 27 February 2012, Vol 134, No. 10, pp. 4445-4468. See the whole document.	1-4,39(2),40(2) ,42-45,55-90,102
<p>-----</p> <p>NOTE: Claims 39 and 40 are found twice. The search has been carried out assuming that the later claims 39 and 40 subsequently followed by the former claims 39 and 40 are considered to be claims 39(2) and 40(2), respectively.</p>		

INTERNATIONAL SEARCH REPORT

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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.: 110-121, 125-128
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 110-121 and 125-128 pertain to methods for treatment of the human body by therapy, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.
2. ☒ Claims Nos.: See Extra Sheet
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:
See the Extra Sheet.
3. ☒ Claims Nos.: See Extra Sheet
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:

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 fee, this Authority did not invite payment of any additional fee.
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.

(Continuation of Box No. II.)

- (2) Claims Nos.: 6, 11-21, 23-37, 40, 47-50, 52, 92, 94, 95, 101, 104-109, 111, 112, 114-121, 123, 124, 127, 128, 131, 132, 134-141.

: The subject matter of claims Nos.: 6, 11-21, 23-37, 40, 47-50, 52, 92, 94, 95, 101, 104-109, 111, 112, 114-121, 123, 124, 127, 128, 131, 132, and 134-141 is so unclear and indefinite that no meaningful search could be made because these claims are drafted in reference to multiple dependent claims which are not drafted in accordance with second and third sentence of Rule 6.4(a) of PCT.

- (3) Claims Nos.: 5, 7-10, 22, 38, 39, 41, 46, 51, 53, 54, 91, 93, 96-100, 103, 110, 113, 122, 125, 126, 129, 130, 133, 142-145.

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