(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 March 2011 (17.03.2011)

PCT

(10) International Publication Number
WO 2011/031896 A3

(51) **International Patent Classification**:
A61K 38/00 (2006.01)

(21) **International Application Number**:
PCT/US2010/048317

(22) **International Filing Date**:
9 September 2010 (09.09.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/240,947 9 September 2009 (09.09.2009) US
61/371,396 6 August 2010 (06.08.2010) 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, 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, PE, PG, PH, PL, PT, RO, RS, RU, 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, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, 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))*

— *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**:
12 May 2011

WO 2011/031896 A3

(54) **Title**: PI3 KINASE INHIBITORS AND USES THEREOF

(57) **Abstract**: The present invention provides compounds, compositions thereof, and methods of using the same.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/48317

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 38/00 (2010.01)
USPC - 514/7.4
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 38/00 (2010.01)
USPC: 514/7.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
IPC(8): A61K 38/00; A61K 43/00, 54/00 (2010.01)
USPC: 514/7.4, 7.5, 2, 12; 424/94.1, 94.3

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST;PGPB, USPT, EPAB, JPAB, Thomson Innovation, GoogleScholar, Dialog
phosphatidylinositol 3-kinase, PIK3, irreversible inhibitor, Cys869 Cys838 Cys815 Cys841 Cys 1119

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Noble et al. Protein Kinase Inhibitors: Insights into Drug Design. Science 303, 1800 (2004) Fig. 2, page 1800, col 3	1-6
Y	Zhang et al. Targeting cancer with small molecule kinase inhibitors. Nature 28 January 2009 Volume 9 page 32 col 2	1-6
Y	Knight et al. Chemically targeting the PI3K family. Biochemical Society Transactions (2007) Volume 35, part 2 245-249 page 241, Fig. 1, page 248 col 1	1-6
Y	Zunder et al. Discovery of drug-resistant and drug-sensitizing mutations in the oncogenic PI3K isoform p110?. Cancer Cell. 2008 August 12; 14(2): 180?192. page 5, first full paragraph, page 18. Fig. 3	1-6
Y	US 2004/0266780 A1 (SADHU et al.) 30 December 2004 (30.12:2004) para[0024]-para[0033]	6
Y	Wissner et al. 2-(Quinazolin-4-ylamino)-[1,4]benzoquinones as Covalent-Binding, Irreversible Inhibitors of the Kinase Domain of Vascular Endothelial Growth Factor Receptor-2. J. Med. Chem., 2005, 48 (24), pp 7560?7581 Abstract	6

☐ 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	Date of mailing of the international search report
3 March 2011 (03.03.2011)	11 MAR 2011
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. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/48317

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

Group I+: Claims 1-45, drawn to a conjugate. Groups I+ contains multiple species of the generic invention. Without payment of an additional search fee, the search will include generic claims (claims 1-5) and the first named species (claim 6). Applicant may have additional species searched for an additional search fee per species. The species are as follows:
-wherein the inhibitor moiety is of formula I (claim 6);
-wherein the inhibitor moiety is of formula II (claims 7-11);
-wherein the inhibitor moiety is of formula III or IV (claims 12-13);
-wherein the inhibitor moiety is of formula V (claim 14);

---------- Continued in Box IV----------

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.:
Claims 1-6

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/US 10/48317

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

---------- Continued from Box II ----------
-wherein the inhibitor moiety is of formula VI (claim 15);
-wherein the inhibitor moiety is of formula VII (claim 16);
-wherein the inhibitor moiety is of formula VIII (claim 17);
-wherein the inhibitor moiety is of formula IX (claim 18);
-wherein the inhibitor moiety is of formula X (claim 19);
-wherein the inhibitor moiety is of formula X (claim 20);
-wherein the inhibitor moiety is of formula XI (claim 21);
wherein the modifier and/or warhead comprises a structure selected from those recited in claims 22-45 (claims 22-45).
Groups II+: Claims 46-54, 344-369, 383 and 344-369, drawn to compounds of formulas I-XXIV, where each invention is limited to a compound of one of formulas I-XII (note that each of formulas XIII-XXIV are examples of formulas I-XII, respectively).
The groups 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
Groups I+ are drawn to a conjugate comprising a PIK protein and an inhibitor. This technical feature is not present in Groups II+ which have special technical features of the compounds of formulas I-XXII.
Although the Groups I+ share the technical feature of claims 1-5, this does not represent an improvement over the following prior art.
-Noble et al. Protein?Kinase Inhibitors: Insights into Drug Design. Science 303, 1800 (2004) Fig. 2, page 1800,?col 3
-Zhang et al. Targeting cancer with small molecule?kinase inhibitors. Nature 28 January 2009 Volume 9 page 32?col 2
-Wissner?et al. 2-(Quinazolin-4-ylamino)-[1,4]benzoquinones as Covalent-Binding, Irreversible Inhibitors of the?Kinase Domain of Vascular Endothelial Growth Factor Receptor-2. J. Med. Chem., 2005, 48 (24), pp 7560?7581 Abstract
-Knight et al. Chemically targeting the?PI3K family. Biochemical Society Transactions (2007) Volume 35, part 2 245-249 page 241, Fig. 1, page 248?col 1
-Zunder?et al. Discovery of drug-resistant and drug-sensitizing mutations in the oncogenic?PI3K?isoform p110?. Cancer Cell. 2008 August 12; 14(2): 180?192. page 5, first full paragraph, page 18. Fig. 3
Regarding claims 1-2, Noble provides background and summary of drug design directed toward the covalent bonding of inhibitors and targeted amino acids such as the covalent bonding between?wortmannin and?Lys833 in?PI3K (Fig. 2) as well as inhibitors 'that bind irreversibly to the?EGFR through covalent bond formation with a?cysteine residue in the ATP pocket are even more effective as?kinase inhibitors (10, 11). Their clinical efficacy is being evaluated.' (page 1800,?col 3).
Zhang corroborates this by teaching that 'clinically most advanced irreversible?kinase inhibitors of the epidermal growth factor receptor (eGFR), HKI-272 ... and CL-387785 were developed to target a relatively rare?cysteine residue located at the lip of the ATP binding site... (page 32?col 2).
The abstract of?Wissner further teaches that the?Cys of the?EGFR is the Cys-1045 (Abstract).
Knight also supports this trend of drug design by providing specifics about?wortmannin which covalently binds to?Lys833 of?PI3K and provides a number of other inhibitors which function by binding to?PI3K amino acids (page 241, Fig. 1) in the ATP pocket (page 248,?col 1).
According to Zunder, Cys-838 is on the site of the ATP competitive pocket where?PI3K inhibitors are located having a higher affinity for that pocket than ATP (page 5, first full paragraph) and is the?Cys in the ATP pocket of?PI3K (page 18. Fig. 3).
It would have been obvious to one of ordinary skill in the art to provide a conjugate of PIK3 and a an inhibitor, as taught by Noble, and to modify the conjugate by replacing the Lys-linkage to Cys-linkage where the Cys is in proximity to the ATP pocket, as suggested by the combined teachings of Noble, Zhang, Wissner, and Night, wherein the Cys-838, as suggested by Zunder, to obtain the inventions as claimed. One would have been motivated to do so in order to provide a more effective kinase inhibitor, as suggested by Noble.
One would have combined the references since they are all directed to inhibiting?kinases by binding inhibitors to particular amino acid residues on a protein. Zhang in particular teaches targeting a?Cys amino acid on the edge of an ATP pocket or EGFR. Zhang additionally teaches the general state of the art such that the concept of linking a?kinase inhibitor to the protein active site is a popular drug approach 'A fourth class of?kinase inhibitors are capable of forming an irreversible, covalent bond to the?kinase active site, most frequently by reacting with a?nucleophilic?cysteine residue.' (page 32?col 2). Given this teaching along with the teaching from Knight for example which teaches that ATP binding pockets of?PI3K are specifically targeted, one of ordinary skill in the art would have found it obvious to target a?Cys on the edge of an ATP pocket of PI3K. Moreover, because of the success of targeting the?Cys on the edge of an ATP pocket such as in Zhang one of ordinary skill in the art would have expected success in treating cancer and other diseases by inhibiting?PI3K in this manner.
Regarding claims 3 and 5, they would have been further obvious because the use of warheads to provide bivalent linkers in conjugates was well known in art.
Regarding claim 4, it would have been further obvious to provide the linkage at Cys862 because Night discloses that hydrogen binding between PI3K and the inhibitor likely occurs Ser854 and a skilled artisan would have selected Cys residues in the vicinity of Ser854 because one would have expected such linkage to position the inhibitor appropriately for binding.
The species of Groups I+ and II+ are limited to different chemical structures which have different structures. Although the several of formulas I-XII share common or similar structures, this does also does not represent an improvement over the prior art as Knight teachers compounds with these common or similar strucutres (pg 247, Fig 1, e.g. ICOS would provide a compound of formula I).

Accordingly, unity of invention is lacking.