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13/926,959	06/25/2013	Guoxian Wu	37JF-193349-US3	1243
117868	7590	09/03/2015	EXAMINER	
Plexxikon Inc. c/o Sheppard Mullin Richter & Hampton LLP 379 Lytton Avenue Palo Alto, CA 94301			WANG, SHENGJUN	
			ART UNIT	PAPER NUMBER
			1627	
			NOTIFICATION DATE	DELIVERY MODE
			09/03/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 13/926,959	Applicant(s) WU ET AL.	
	Examiner SHENGJUN WANG	Art Unit 1627	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8/3/2015.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 1-3,7,8,10,16 and 18-20 is/are pending in the application.
5a) Of the above claim(s) 19 and 20 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 1-3,7,8,10,16,18 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 3) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b)
Paper No(s)/Mail Date ____. | 4) <input type="checkbox"/> Other: ____. |

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The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Receipt of applicants' amendments and remarks submitted August 3, 2015 is acknowledged.

Claim Rejections 35 U.S.C. 112

1. The following is a quotation of 35 U.S.C. 112(a):

(a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), first paragraph:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-3, 7, 8, 10, 16 and 18 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.
3. The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:
4. "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.

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1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966. *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

5. Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

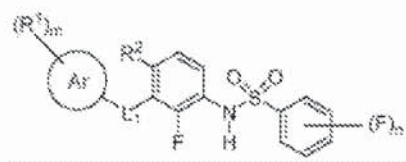
6. The MPEP states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

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7. The Guidelines for Examination of Patent Applications Under 35 USC 112, ¶1, "Written Description" Requirement (Federal Register, Vol. 66, No. 4, pg. 1105, column 3), in accordance with MPEP § 2163, specifically state that for each claim drawn to a genus the written description requirement may be satisfied through sufficient description of a representative number of species by a) actual reduction to practice; b) reduction to drawings or structural chemical formulas; c) disclosure of relevant, identifying characteristics (i.e. structure) by functional characteristics coupled with a known or disclosed correlation between function and structure. The analysis of whether the specification complies with the written description requirement calls for the examiner to compare the scope of the claim with the scope of the description to determine whether applicant has demonstrated possession of the claimed invention (Federal Register, Vol. 66, No. 4, p. 1105, 3rd column, 3rd paragraph). Below is such comparison.

8. Scope of claims (elected invention):

A compound of formula (Ia):



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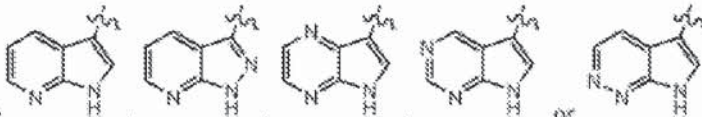

or a pharmaceutically acceptable salt thereof,

wherein:

L_1 is a bond, $-N(R^{11})-$, $-N(R^{11})-C(X)-$, $-N(R^{11})-S(O)_2-$, $-N(R^{11})-C(NH)-$, $-N(R^{11})-C(X)-N(R^{11})-$, or $-N(R^{11})-S(O)_2-N(R^{11})-$;

 X is O[[or S]]; R^{11} is hydrogen or optionally substituted lower alkyl;each R^1 is optionally substituted lower alkyl or optionally substituted heteroaryl; R^2 is hydrogen, lower alkyl, or halogen; n is 1 or 2; R^3 is optionally substituted aryl; R^4 is hydrogen;the subscript m is 0, 1, 2, 3, 4, or 5; and

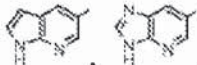
Ar is optionally substituted nitrogen-containing heteroaryl, with the proviso that Ar is

other than , wherein  indicates the point of the attachment to L_1 the phenyl moiety in formula (Ia).

and pharmaceutical composition comprising the compound, pharmaceutical acceptable excipients, and additional active agents

Scope of disclosure**Reduction to Practice**

The compounds reduced to practice support the following:

Ar is , wherein L_1 is $-C(O)NH-$;

Ar is , wherein L_1 is $-C(O)NH-$ or $-NHC(O)-$;

Reduction to structural of chemical formulas:

The only disclosure, is in the form of general formula with lists of possible groups. See, Formula I, paragraph [0005] and formula Ic, paragraph [0015]. This kind of disclosure is not representation of any species. A "laundry list" disclosure of every possible moiety does not

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constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species. MPEP 2163.1.A. and *Fujikawa v. Wattanasin*, 93 "3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed.Cir. 1996). Therefore, there is no species (e.g., by reduction to structural/chemical formulas) in addition to those reduced to practice.

Correlation between Structure and Function."

A correlation between structure and function, for the instantly claimed genus of compounds, is neither known in the art nor disclosed in the specification. All disclosed compounds have a linker moiety between the phenyl and the Ar. i.e., L1 in formula I is not a bond. The application provide no convincing evidence, or rationale that the biological activity of disclosed compounds would have been retained if the L1 in formula I is a bond instead of those linking moieties. Thus, it is not understood what specific structures for the claimed variables will lead to compounds that have the instantly claimed activity.

III. *Analysis of Fulfillment of" Written Description Requirement:*

The structure/activity relationship (SAR) for binding and activity is elucidated upon analysis of IC₅₀ data of multiple compounds with various types of structural modifications. These types of studies provide insight into the structural limitations that are required for activity, i.e. specific structural elements tolerated for the claimed activity. In the absence of such correlation, it is not possible to determine what structural modifications will allow for the preservation of the desired activity.

In conclusion: (i) substantial structural variation exists in the genus/subgenus embraced by claims 1-3, 7, 8, 10, 16 and 18; (ii) No disclosure of species supporting the genus; (iii) common

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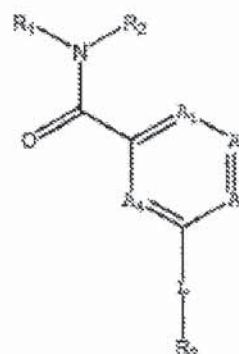
structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function, is neither disclosed in the instant application nor commonly known in the art. Thus, the specification fails to provide adequate written description for the genus of compounds claimed and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections 35 U.S.C. 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 1-8, 10, 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dimauro et al. (WO 2007/022380, IDS).



11. Dimauro et al. teach compounds having a general formula of

A^1 is CH^6 or N ;

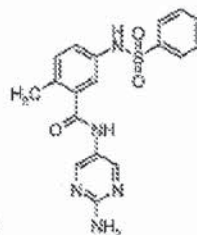
A^2 is CH^6 or N ;

A^3 is CR^6 or N ;

wherein A^4 is CR^7 or N , R^1 is a pyridyl, or pyrimidinyl, wherein the

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pyridyl or pyrimidinyl may be further substituted with various substituents, L is $-NR_7S(O)_2-$; R₃ is alkyl, or aryl, see pages 26-31, and each of R₄, R₅, R₆ and R₇ may be hydrogen, alkyl,



or halogens. Expressly disclosed compounds include compound 93 . See, page

114. The compounds are useful for modulating the activity of protein cytokinase and for treating cytokinase mediated disease. See, particularly, the abstract, and the claims.

12. Dimauro et al. do not teach expressly a compound that is within the scope of claimed invention, such as wherein A₄ is CR₇, R₄ and R₇ is fluoro, and or wherein the R₃ is pyridyl.

13. However, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to make a compound according to the general formula of Dimauro et al. wherein CR₇, R₇ is halogen, such as fluoro and R₃ is pyridyl, i.e., replace the hydrogen group in compound 93 with a fluoro and replace the pyrimidinyl with pyridyl.

14. A person of ordinary skill in the art would have been motivated to make a compound according to the general formula of Dimauro et al. wherein CR₇, R₇ is halogen, such as fluoro and R₃ is pyridyl, i.e., replace the hydrogen in compound 93 with a fluoro and replace the pyrimidinyl with pyridyl, because Dimauro et al. discloses that halogen and hydrogen are interchangeable at the particular position, pyrimidinyl and pyridyl are also interchangeable at the particular position. One of ordinary skill in the art would have reasonably expected that such a compound be active as protein cytokinase modulator.

Response to the Arguments

15. Applicants' amendments, exhibits and remarks submitted August 3, 2015 have been fully considered, but found unpersuasive as to the rejections set forth above.

16. Applicants contend that specification does not need to provide an example for very permutation, and that "certain corrections between structure and function were known in the art" citing Liu et al. and Tsai et al. Applicants also argue that fluoro-substituted phenyl ring connected between an aryl group and a sulfonamide can interact with particular hydrophobic pocket of B-Raf kinase and therefore, a correlation between structure and function was in the art.

17. The arguments are not probative. Applicants fail to address the compounds structure as whole encompassed within the claim. Particularly, the structure of Ar moiety which defined broadly as to encompass all nitrogen containing heteroaryl with the exception of five structures therein. Ar encompasses all those nitrogen-containing heteroaryl structures with distinct size, polarity, and shapes. The specification or the prior art does not provide evidence and rationale that such distinct moiety will provide similar binding activity to protein kinases in general, and B-Raf kinase in particular.

18. Applicants' remarks regarding the rejections under 35 U.S.C. 103 are untenable. First, "Lead compound" arguments are not applicable herein. In both *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.* and *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, the compounds at issue is a single compound with established, superior properties. Contrary to *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.* and *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, claims herein are drawn to a general formula encompassing thousands of compounds without evidence substantiating superior/unexpected benefit. Further, Dimauro et al. teach specifically that the R3 may be

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aromatic ring which may be optional substituted and substituents may be halogen, such as chloro, fluoro. See, e.g. the claims. Therefore, the claims herein at least overlap in scope with those disclosed in Dimauro et al. With the examples expressly disclosed therein, such as examples 93 (sulfonamide), 297, 298 (fluoro-phenyl) and the general instruction provided therein, one of ordinary skill in the art would have sufficient teachings, suggestions and motivation to reach the claimed invention herein. Furthermore, as applicants argued, “certain corrections between structure and function were known in the art”, such as fluoro-substituted phenyl ring connected between an aryl group and a sulfonamide can interact with a binding site of protein kinases are known (see, page 7 bridging page 8 of the response filed August 3, 2015). Therefore, one of ordinary skill in the art would have been motivated to select a hydrophobic moiety such as fluorophenyl for making protein kinase inhibitors.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHENGJUN WANG whose telephone number is (571)272-0632.

The examiner can normally be reached on Monday to Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://portal.uspto.gov/external/portal>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHENGJUN WANG/
Primary Examiner, Art Unit 1627