

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor(s): Guoxian Wu, et al.
Appl. No.: 13/926,959
Title: COMPOUNDS AND METHODS FOR KINASE
MODULATION, AND INDICATIONS THEREFOR
Filing Date: 06/25/2013
Examiner: Wang, Shengjun
Art Unit: 1627
Confirmation Number 1243

AMENDMENT AND REPLY UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Amendment and Reply is responsive to the Non-Final Office Action dated April 3, 2015, concerning the above-referenced patent application. The Office set a three-month period to reply. Accordingly, this Amendment and Reply is timely filed, along with a one month extension of time, on or before its due date of August 3, 2015.

Amendments to the Claims are reflected in the **Listing of Claims**, which begins on page 2 of this document.

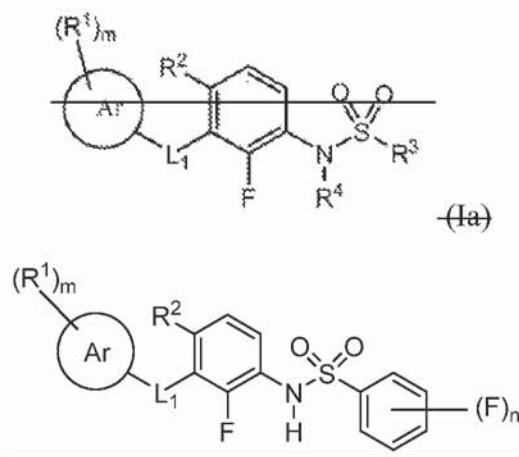
Remarks/Arguments begin on page 5 of this document.

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A compound of formula (Ia):



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;

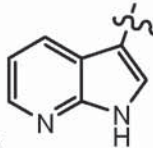
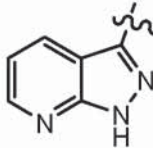
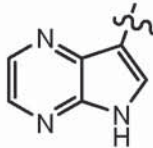
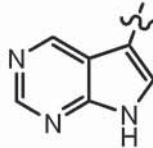
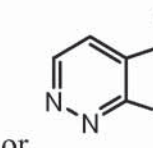

R^2 is hydrogen, lower alkyl, or halogen;

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 , , ,  or , wherein , indicates the point of the attachment to ~~L₁ the phenyl moiety in formula (Ia).~~

2. (Original) The compound of claim 1, wherein R² is hydrogen.
3. (Original) The compound of claim 2, wherein R² is halogen.
- 4.-6. (Canceled).
7. (Currently Amended) The compound of claim 1[[6]], wherein ~~R² is phenyl~~ substituted with two fluoro substituents n is 2.
8. (Previously Presented) The compound of claim 1, wherein each R¹ is optionally substituted lower alkyl.
9. (Canceled).
10. (Previously Presented) The compound of claim 1, wherein each R¹ is optionally substituted heteroaryl.
- 11.-15. (Canceled).
16. (Original) A pharmaceutical composition comprising: a compound of claim 1 and a pharmaceutically acceptable carrier or excipient.
17. (Canceled).
18. (Original) A pharmaceutical composition comprising a compound of claim 1 and another therapeutic agent.

19. (Withdrawn) A method for treating a subject suffering from melanoma, thyroid cancer or colorectal cancer, said method comprising: administering to the subject an effective amount of a compound of claim **1**.

20. (Withdrawn) The method of claim **19**, wherein the melanoma is melanoma having a mutation encoding a V600E amino acid substitution.

REMARKS

Applicant respectfully requests that the foregoing amendments be made in the present application.

Claim Amendments

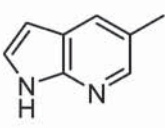
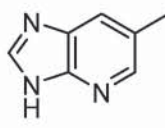
Claims 19-20 are withdrawn, and claims 9, 11-15, and 17 were previously canceled. By this paper, claims 1 and 7 are amended, and claims 4-6 are canceled. Support for the amendments can be found throughout the original claims and specification as filed, such as paragraphs [0005], [0041], [0048], and [0091] and compounds provided in, for example, paragraph [0234]. No new matter has been added by these amendments, and as such, Applicant respectfully requests its entry. Applicant reserves the right to pursue canceled subject matter in a continuing application.

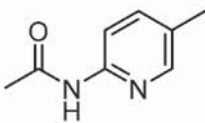
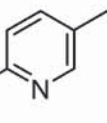
Rejection under 35 U.S.C. § 112, Written Description

Claims 1-5, 8, 9, 11, 19-26, and 28-29 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office alleges that substantial structural variation exists in the claimed genus/subgenus, there is no disclosure of species supporting the genus, and common structural attributes of the claimed genus/subgenus, combined with a correlation between structure and function is neither disclosed in the present application or commonly known in the art. Office Action at p. 7.

The Examiner bears the initial burden of presenting evidence why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. M.P.E.P. § 2163.04. While the Office cites *In re Gostelli* for the proposition that "the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus" (Office Action at p. 4), Applicant notes that M.P.E.P. § 2163(II)(A)(3)(a)(ii) also provides that "there may be situations where one species adequately supports a genus." If the disclosure indicates that the patentee has invented species sufficient to constituted the genus, the disclosure of only one species encompassed within a genus can adequately describe the claim. *Id.*

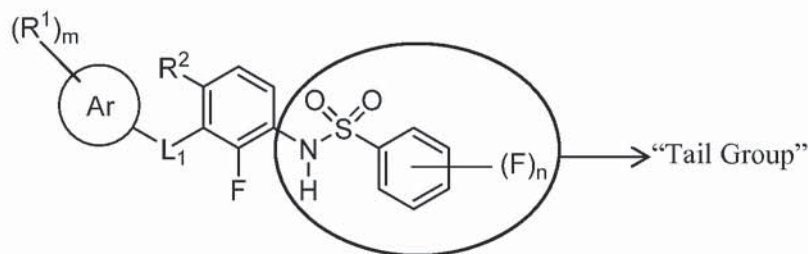
The Office has acknowledged that the compounds reduced to practice in the specification

supports the following compounds: Ar is  and , wherein L₁ is –

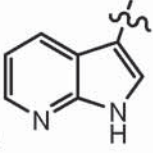
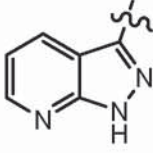
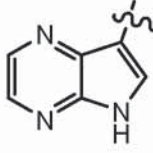
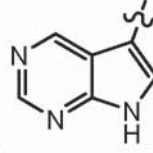
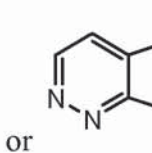
 C(O)NH-; and Ar is , wherein L₁ is –C(O)NH- or –NHC(O)-. Office Action at p. 5.

However, the Office alleges that “there is no species (e.g., by reduction to structural/chemical formulas) in addition to those reduced to practice.” Office Action at p. 6. Additionally, the Office alleges that “[a]ll disclosed compounds have a linker moiety between the phenyl and the Ar, i.e., L₁ in formula I is not a bond.” Office Action at p. 6. However, “[d]escription of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.” M.P.E.P. §2163(II)(A)(3)(a)(ii).

Applicant submits that the Office has not met their burden and in fact, Applicant was in clear possession of the invention at the time of filing. However, in a sincere attempt to expedite prosecution, the claims have been amended to be directed to a more focused genus of compounds having the following formula:



wherein Ar is a nitrogen containing heteroaryl, R¹ is optionally substituted lower alkyl or optionally substituted heteroaryl; m is 0, 1, 2, 3, 4, or 5; R² is hydrogen, lower alkyl, or halogen; n is 1 or 2; L₁ is a bond, -N(R¹¹)-, -N(R¹¹)-C(X)-, -N(R¹¹)-S(O)₂-, -N(R¹¹)-C(NH)-, -N(R¹¹)-C(X)-N(R¹¹)-, or -N(R¹¹)-S(O)₂-N(R¹¹)-; X is O; and R¹¹ is hydrogen; with the proviso that Ar is

other than , , ,  or . As can be seen, the compounds require a sulfonamide group connected to two fluoro-substituted phenyl rings and include a “tail group” as discussed further below.

The present application also discloses numerous exemplary compounds falling within the claimed genus, such as throughout Examples 1 to 12. Applicant respectfully submits that its disclosure of numerous exemplified compounds provide a representative number of species to satisfy the written description requirement for the currently claimed genus.

The Office further alleges that “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.” Office Action at p. 7. Applicant respectfully disagrees. The specification does not need to provide an example of every permutation to meet the written description requirement. *See* M.P.E.P. §2163(II)(A)(3)(a)(ii).

Additionally, certain correlations between structure and function were known in the art. Specifically, prior to the filing of the present application, interactions between protein kinases and similar compounds to the claimed compounds were known. For example, interactions between specific areas of kinases and a compound’s “tail group” (corresponding to the substituted benzenesulfonamide group as shown circled in the schematic above), including at least the binding of a “tail group” within certain pockets of kinases, were known. *See, e.g.*, p. 360 of Liu et al., *Nature Chem. Bio.*, 2006, 2(7), 358-364 (copy submitted as **Exhibit A**); *see also* p. 3043 of Tsai et al., *PNAS*, 2008, 105(8), 3041-3046 (citing Wan et al., *Cell*, 2004, 116(6), 855-867)(copy submitted as **Exhibit B**). Hydrogen bonding and hydrophobic interactions were also known to be involved in a compound’s binding to kinases. *See, e.g.*, p. 358-360 of **Exhibit A**.

Moreover, the present application discloses that compounds described therein are active on Raf protein kinases (*see* paragraph [0003]), and the claimed compounds comprise moieties that are involved with the compounds’ binding to B-Raf kinase. For example, a fluoro-substituted phenyl ring connected between an aryl group and a sulfonamide can interact with a

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particular hydrophobic pocket of a B-Raf kinase. *See, e.g.*, page 3042 of **Exhibit B**. Nitrogen and oxygen atoms of a sulfonamide also can be involved in key interactions with various amino acids of B-Raf kinase. *Id.* at p. 3043. Further, a “tail group” of a compound can also affect its binding to B-Raf kinase. *See, e.g., id.* at p. 3043.

Thus, a correlation between structure and function was known in the art such that it can be understood what structural features will lead to compounds with activity. Compounds that include structural features already demonstrated to be involved in binding with kinases are disclosed in the present application.

Accordingly, in view of the disclosure of the present application and what was known in the art as discussed above, the present specification sufficiently describes the presently claimed subject matter to reasonably convey to one of ordinary skill in the art that the Applicant had possession of the claimed invention. Applicant requests that the rejection be withdrawn.

Rejections under the Judicially Created Doctrine of Improper Markush Grouping

Claims 1-8, 10, 16, and 18 stand rejected on the judicially-created basis that it contains an improper Markush grouping of alternatives. The Office states that the improper Markush grouping includes species of the claimed invention that do not share both a substantial structural feature and a common use that flows from the substantial structural feature. The Office further alleges that the instant claims read on numerous possible distinct species, and there is no substantial structural feature shared by all species. Office Action at p. 8.

To the extent the rejection applies to the present claims, Applicant traverses the rejection.

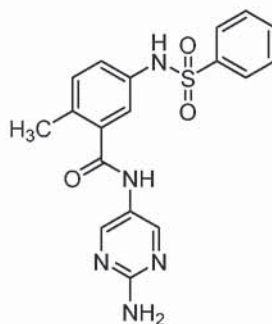
As discussed above, the claimed compounds require two fluoro-substituted phenyl groups, one of which is further substituted with L_1 -Ar and R^2 , connected via a sulfonamide. Thus, the claimed compounds share a substantial structural feature, and those features are related to activity as discussed above.

Further, the claimed compounds are useful as kinase inhibitors. Pages 1-2 of the specification. As discussed above, the sulfonamide and its flanking fluoro-substituted phenyl groups of the claimed compounds can be involved in interactions with a target kinase. Thus, a common use flows from the substantial structural feature.

Accordingly, because the recited claims satisfy both the “single structural similarity” and “common use” prongs of the Markush grouping standard, Applicant respectfully requests withdrawal of the improper Markush grouping rejection.

Rejection under 35 U.S.C. § 103

Claims 1-8, 10, 16, and 18 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Dimauro et al. (WO 2007/022380). The Office asserts that “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 . . .” Office Action at p. 10. Compound 93 is shown below:



To the extent the rejection applies to the present claims, Applicant traverses the rejection.

Specifically, Applicant submits that the Office Action has not established a *prima facie* case of obviousness as the standard employed in the Office Action is incorrect. If the correct lead compound analysis required by recent Federal Circuit decisions is applied, a *prima facie* obviousness cannot be established. As such, Applicant is “under no obligation to submit evidence of nonobviousness.” MPEP § 2142.

The Correct Legal Standard of Determining Obviousness Is Not Employed in the Office Action

The Office's obviousness allegation is solely based on rationales that have been rejected by the Office's own guideline as being sufficient to establish a *prima facie* case of obviousness. The structure similarity rationale is not sufficient to support an obviousness rejection.

First, the MPEP expressly rejects the above alleged motivation given in the Office Action in establishing obviousness, stating that "[t]he fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." MPEP § 2144.08 (citing *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994), *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) and *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995)).

Second, the MPEP also expressly rejects the notion that structure similarity alone is sufficient to show obviousness stating that even "[h]omology should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed 'as a whole.'" MPEP § 2144.09 (citing *re Langer*, 465 F.2d 896, 175 USPQ 169 (CCPA 1972)).

Thus, the obviousness rejection is not supported by sufficient legal basis. Rather, under the standard established by Federal Circuit case law, a lead compound analysis is required when determining obviousness for chemical compounds.

Lead Compound Analysis Required by the Federal Circuit in Determining Obviousness of Chemical Compounds

The lead compound analysis is a two-step analysis. First, "*prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). It requires a demonstration "that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art."

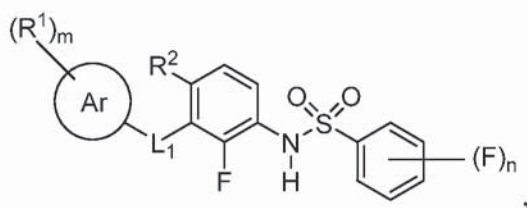
Daiichi Sankyo Co. v. Matrix Laboratories Ltd., 96 USPQ2d 1526, 1533 (Fed. Cir. 2010).

Second, after a lead compound has been identified, a determination is required as to whether “the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound.”

Eisai, 533 F.3d at 1359.

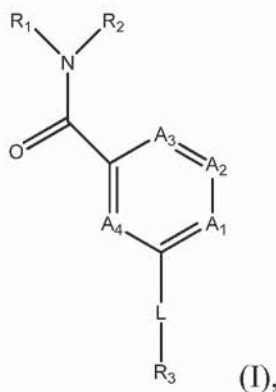
Applicant submits that the claimed compounds are not obvious under the lead compound analysis.

As discussed above, the presently claimed compounds are of formula:



wherein the variables are as delineated above.

Dimauro et al. teaches a broad genus of compounds of formula (I):



wherein the variables are selected from a variety of substituents (see, pages 11-16).¹ Dimauro et al. not only teaches the above broad genus covering a vast number of compounds, but also teaches approximately 400 specifically exemplified compounds, majority of which have L as -NHC(O)-. Only a few compounds contain L as -NHSO₂-. See, for example, page 113-114

¹ Dimauro et al. also teaches a broad genus of compounds of formula (II), wherein the C(O)NR₁R₂ and LR₃ are para to each other. Several specific compounds of formula (II) are disclosed in Table 1 on pages 152-156. Applicant has focused the arguments on formula (I) as formula (II) is not relevant to the claimed invention.

and compounds 345, 346, and 350 on page 159. Further, Dimauro et al. teaches compounds wherein A₄ is always CH or C-CH₃, whereas the instant claims *require* A₄ to be CF.

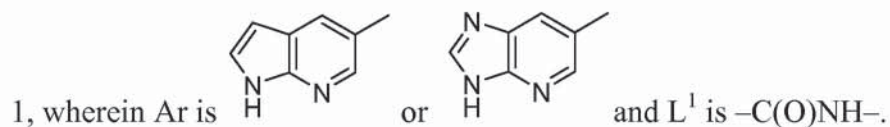
The claimed compounds are not obvious as Dimauro et al. does not teach or suggest, and the Office Action has not stated any rational basis for a person skilled in the art to determine, what is or are the lead compound(s) out of the numerous compounds taught in Dimauro et al. The selection of claimed compounds as the lead compounds in the Office Action can only be based on impermissible hindsight view of the teachings of the instant application.

Based on the teachings of Dimauro et al., one of skill in the art would not arrive at the instant claims because one will have to pick and choose from the almost infinite number of possibilities of the substituents, and Dimauro et al. does not provide any motivation to pick and choose the specific substituents of the claimed invention. Assuming *arguendo* one of skill in the art were to pick and choose from the specific teaching of Dimauro et al., one would never arrive at the claimed invention because Dimauro et al. does not teach a single compound that contains the specific fluoro-substituted phenyl ring, let alone the combination of the sulfonamide group flanked by fluoro-substituted phenyl rings.

Thus, Dimauro et al. has not identified a lead compound. Assuming *arguendo*, a lead compound is a compound without the fluoro substituent at A₄ and without the sulfonamide as the L, there is no motivation provided in Dimauro et al. to add these specific substituents to arrive at the claimed compounds. Therefore, Dimauro et al. fails both prongs of the lead compound analysis. Thus, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant respectfully requests withdrawal of the rejection.

Allowable Subject Matter

Applicant thanks the Office for acknowledging the patentability of compounds of claim



Applicant believes that the present application is now in condition for allowance. Accordingly, reconsideration and favorable action on all claims are respectfully requested. In the event any issues remain to be resolved in view of this communication, the Examiner is invited to contact the undersigned at the telephone number set forth below so that a prompt disposition of the present application can be achieved.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-6219. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-6219.

Respectfully submitted,

Date August 3, 2015

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