2019 PAT. APP. LEXIS 9373

Patent Trial and Appeal Board

August 21, 2019, Decided

Appeal 2018-001199 ; Application 14/257,347 ; Technology Center 1600

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

Reporter
2019 PAT. APP. LEXIS 9373 *

Ex parte CHENGZHI ZHANG

Notice:

[*1] ROUTINE OPINION. Pursuant to the Patent Trial and Appeal Board Standard Operating Procedure 2, the opinion below has been designated a routine opinion.

Core Terms

compound, deuteration, metabolic, enrich, teach, metabolite, dosage unit, prior art, nilotinib, plasma, decrease, non-isotopically, skill, deuterium, predictable, disclosure, kinase, modify, salt

Panel: Before DONALD E. ADAMS, JEFFREY N. FREDMAN, and ULRIKE W. JENKS, Administrative Patent Judges.

Opinion By: JEFFREY N. FREDMAN

Opinion

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal [1], [2] under 35 U.S.C. § 134 involving claims to substituted aminopyrimidine compounds. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

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[1] Appellant identifies the Real Party in Interest as Teva Pharmaceutical Industries Ltd. (*See* App. Br. 1).

[2] We have considered and refer to the Specification of Apr. 21, 2014 ("Spec."); Final Office Action of May 26, 2016 ("Final Action"); Appeal Brief of Jan. 4, 2017 ("App. Br."); Examiner's Answer of Sept. 22, 2017 ("Ans."); and Reply Brief of Nov. 15, 2017 ("Reply Br.").

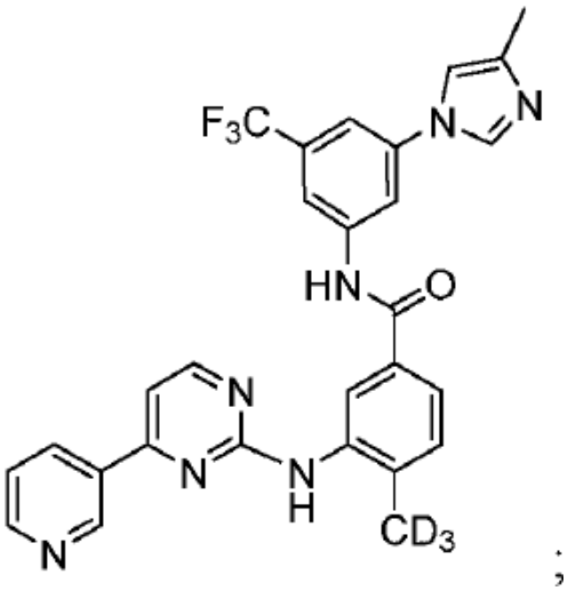
"Nilotinib . . . is a tyrosine kinase inhibitor. Nilotinib is commonly prescribed for the treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myeloid leukemia" (Spec. P 3). However, "[n]ilotinib undergoes extensive oxidative metabolism via CYP3A4, and to a lesser degree by CYP2C8, CYP2C9, and CYP2D6" (*id.* P 4). These cytochrome enzymes "react with and convert [] foreign substances to more polar intermediates or metabolites for renal excretion. Such metabolic reactions frequently involve the oxidation of a carbon-hydrogen (C-H) bond" (*id.* P 5).

"Deuterium (2H or D) is a stable and non-radioactive isotope **[*2]** of hydrogen" and "substituting a deuterium for [a] protium will cause a decrease in the reaction rate" because "a C-D bond is stronger than the corresponding C-<1>H bond" (*id.* PP 8-9). "Deuteration of pharmaceuticals to improve pharmacokinetics (PK), pharmacodynamics (PD), and toxicity profiles has been demonstrated previously with some classes of drugs" (*id.* P 11). "[N]ilotinib is metabolized in humans at the imidazole and phenyl methyl groups, the imidazole ring, and the trifluomethyl-bearing phenyl ring. The current approach has the potential to prevent metabolism at these sites" (*id.* P 13).

The Claims

Claims 2, 4-6, 14, and 21-41 are on appeal. Claim 14 is the sole independent claim and reads as follows:

14. A compound that is



wherein at least one position designed as D as a deuterium enrichment of no less than about 10%;

or a pharmaceutically acceptable salt thereof.

The Rejections

The Examiner rejected claims 2, 4-6, 14, 21-27, 32, and 34-41 under 35 U.S.C. § 103(a) as obvious over Manley, [3] Breitenstein, [4] Gant '965, [5] Gant '622, [6] Gant '734, [7] Gant '026, [8] Gant '247, [9] Gant '316, [10] Gant '991, [11] Gant '886, [12] Gant '071, [13] Gant '200, [14] Gant '036, [15] and Gant '555 [16] (Ans. 2-4).

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[3] Manley et al., WO 2007/015871 A1, published Feb. 8, 2007.

[4] Breitenstein et al., WO 2004/005281 A1, published Jan. 15, 2004.

[5] Gant et al., US 2007/0281965 A1, published Dec. 6, 2007.

[6] Gant et al., US 2007/0149622 A1, published June 28, 2007.

[7] Gant et al., US 2007/0287734 A1, published Dec. 13, 2007.

The Examiner rejected claims 14, 22, 24, 25, 28-31, and 33 under 35 U.S.C. § 103(a) as obvious over Manley, Breitenstein, Gant, and Lewis [17] (Ans. 5-6).

The Examiner finds Manley teaches "the hydrochloride monohydrate salt of the compound of Formula I" (Final Act. 4). The Examiner finds Breitenstein teaches "the compound of Formula I" and "discloses methods of treating tyrosine kinase-mediated disorders (pp. 32-33), such as Philadelphia-positive chronic myelogenous leukemia" (*id.*).

The Examiner acknowledges "these references do not specifically disclose the deuterium-enriched compounds of Formula I" (Final Act. 4). The Examiner finds Gant [18] teaches "deuterium-enriched zolpidem, venlafaxine, rimonabant, pirfenidone, ranolazine, phenylephrine, agomelatine, pimavanserin, ketamine, ilaprazole, sitaxsentan, and losartan" (Final Act. 4).

The Examiner finds "one skilled in the art would have been motivated to deuterate the compound of either Manley et al. or Breitenstein et al. in order to take advantage of improvements in pharmacological properties that deuterium substitution affords" (Final Act. 5).

The issue with respect to this rejection is: Does a preponderance of the evidence of record support the Examiner's conclusion that the prior art suggests the claimed compound?

Findings of Fact

1. Manley teaches "protein kinase inhibitor useful in therapy for diseases which respond to inhibition of protein kinase activity" (Manley P 2).

2. Manley teaches preparation of the monohydrochloride monohydrate salt of a kinase inhibitor as shown below:

Manley teaches a process "to obtain 4-methyl-N-[3-(4-methyl-imidazol-1-yl)-5-trifluoromethyl-phenyl]-3-(4-pyridin-3-yl-pyrimidin-2-ylamino)-benzamide **[*5]** monohydrochloride monohydrate salt" (Manley PP 34-35).

3. Breitenstein teaches "a method for the treatment of leukaemia which responds to an inhibition of the Abl tyrosine kinase activity, which comprises administering a compound of formula I or a N-oxide or a pharmaceutically acceptable salt thereof" (Breitenstein 32).

4. Breitenstein teaches a process of making "4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]- *N*-[5-(4-methyl-1H-imidazol-1-yl)-3-(trifluoromethyl)phenyllbenzamide" (Breitenstein 63).

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[8] Gant et al., US 2008/0319026 A1, published Dec. 25, 2008.

[9] Gant et al., US 2008/0312247 A1, published Dec. 18, 2008.

[10] Gant et al., US 2008/0300316 A1, published Dec. 4, 2008.

[11] Gant et al., US 2008/0280991 A1, published **[*3]** Nov. 13, 2008.

[12] Gant et al., US 2008/0280886 A1, published Nov. 13, 2008.

[13] Gant et al., US 2008/0268071 A1, published Oct. 30, 2008.

[14] Gant et al., US 2008/0255200 A1, published Oct. 16, 2008.

[15] Gant et al., US 2008/0255036 A1, published Oct. 16, 2008.

[16] Gant et al., US 2008/0132555 A1, published June 5, 2008.

[17] Lewis et al., WO 2004/103344 A1, published Dec. 2, 2004.

[18] Because only specific citation by paragraph in the rejection is to the Gant '555 publication, **[*4]** we will limit our review to that publication. *See* 37 C.F.R. § 1.104(c)(2) ("[T]he particular part [of the prior art] relied on must be designated as nearly as practicable.")

5. Gant '555 teaches:

> The deuterated analogs of this invention have the potential to uniquely maintain the beneficial aspects of the non-isotopically6 enriched drugs while substantially increasing the half-life (T[1/2]), lowering the maximum plasma concentration (C *[max]*) of the minimum efficacious dose (MED), lowering the efficacious dose and thus decreasing the non-mechanism-related toxicity, and/or lowering the probability of drug-drug interactions.

(Gant '555 P 90).

6. Gant '555 teaches compounds that have properties including:

> a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the nonisotopically enriched compound; b) **[*6]** increased average plasma levels of said compound per dosage unit thereof as compared to the nonisotopically enriched compound; c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; d) increased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound. In yet further embodiments said compound has at least two of the following properties: a) decreased inter-individual variation in plasma levels of said compound or a metabolite thereof as compared to the nonisotopically enriched compound; b) increased average plasma levels of said compound per dosage unit thereof as compared to the nonisotopically enriched compound; c) decreased average plasma levels of at least one metabolite of said compound per dosage unit thereof as compared to the non-isotopically enriched compound; and d) increased average plasma levels of at least one metabolite of said compound **[*7]** per dosage unit thereof as compared to the non-isotopically enriched compound; and e) an improved clinical effect during the treatment in said subject per dosage unit thereof as compared to the non-isotopically enriched compound. In yet further embodiments said compound has a decreased metabolism by at least one polymorphically-expressed cytochrome P[450] isoform in said subject per dosage unit thereof as compared to the non-isotopically enriched compound.

(Gant '555 PP 27-39; paragraph numbers omitted).

7. Gant teaches "deuterium incorporation can lead to metabolic switching" and "[m]etabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and are not predictable a priori for any drug class" (Gant '555 P 87).

Principles of Law

Under the lead compound analysis rubric, we must first "determine[] whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). "The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation **[*8]** to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Id.* at 1292.

A prima facie case for obviousness requires "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

Analysis

Appellant contends the "Examiner has failed to articulate a single reason why one of ordinary skill in the art would have deuterated any of Breitenstein's or Manley's compounds" (App. Br. 5). Appellant contends8 the "cited art does not disclose or suggest that nilotinib could benefit from chemical modification. Significantly, neither reference suggests that nilotinib possesses any metabolic or other pharmacokinetic deficiencies" (App. Br. 6). Appellant also

contends the "Examiner provides no rationale as to why the person of ordinary skill in the art would have selected the particular C-<1>H bonds for substitution with C-<2>H bonds, to arrive at the particular d[3] analogue claimed" (App. Br. 7). Lastly, Appellant provides a number of disclosures showing "the unpredictable consequences of deuteration" (App. Br. 9-12) including that "Nevirapine deuteration resulted in increased **[*9]** metabolism, rather than decreased metabolism" (App. Br. 12).

The Examiner states, in the context of substituting equivalents that "there is no requirement that the examiner must provide a specific rationale to select one compound over another" (Ans. 7). The Examiner states that "it is the examiner's position that deuteration of nilotinib is prima facie obvious per se. On the other hand, figuring out which of the 22 hydrogen atoms to substitute for deuterium would have been a matter of routine experimentation" (Ans. 8). The Examiner also states that the Gant references "would have provided motivation to the skilled artisan to make deuterium-substituted nilotinib in order to take advantage of the favorable properties that this modification would be expected to produce" (Ans. 9). We agree with Appellant. The Examiner is incorrect on the legal standard for obviousness because "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Whether in the context of substituting known equivalents or in providing motivation, the **[*10]** burden is on the Examiner to establish a prima facie case. There is no such thing as "prima facie obvious per se." We do not disagree that express reasons for substituting equivalents need not be present, but "[i]n order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents." MPEP § 2144.06(II). The Examiner has not provided any evidence that any of the deuterated compounds of Gant are functionally equivalent to the specific compound of claim 14 nor has the Examiner provided any evidence of any structural similarity.

If we apply the lead compound analysis, we might agree with the Examiner that nilotinib is a reasonable lead compound based on the teachings of Manley and Breitenstein (FF 1-4) and that Gant provides several generic reasons to modify nilotinib by deuteration (FF 5-6). However, claim 14 is not a generic modification of nilotinib by deuteration but rather is a modification of a particular position on the molecule. The Examiner provides no reason to make the particular **[*11]** modification required.

In contrast, Appellant has provided a number of disclosures demonstrating that deuteration of different chemicals yields unpredictable results [19] (*see* App. Br. 9-12), consistent with the disclosure in the Specification that deuteration may yield a "new metabolic profile [that] may impart more or less toxicity. Such pitfalls are non-obvious and are not predictable *a priori* for any drug class" (Spec. P 11). Gant '555 provides a similar disclosure, teaching that "deuterium incorporation can lead to metabolic switching" and "[m]etabolic switching can potentially lead to different proportions of known metabolites as well as altogether new metabolites. This new metabolic profile may impart more or less toxicity. Such pitfalls are non-obvious and are not predictable a priori for any drug class" (FF 7).

While *O'Farrell* states that "[o]bviousness does not require absolute predictability of success," *O'Farrell* identifies

> two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible **[*12]** choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988) (citations omitted). The instant situation fits *O'Farrell's* second kind of error, since the prior art of Gant '555 at best provides general guidance that deuteration of molecules may

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[19] We recognize that the Specification lacks any working examples, but the current rejection is for obviousness, not enablement.

sometimes improve their properties (FF 5-6). While deuteration might represent a promising field of experimentation, Gant '555 itself demonstrates that the results of deuteration are not predictable (FF 7). There is also no persuasive evidence that the experimentation required to identify a deuterated nilotinib would have been merely routine as asserted by the Examiner (*see* Ans. 8).11

Therefore, because the Examiner provides no reason or evidence to deuterate the particular position of nilotinib required by claim 14 and because the **[*13]** Specification and Gant '555 evidence the unpredictability of deuteration, we find the evidence does not support a finding of a reasonable expectation of success.

Conclusion of Law

A preponderance of the evidence of record does not support the Examiner's conclusion that the prior art suggests the claimed compound.

SUMMARY

In summary, we reverse the obviousness rejections.

REVERSED

USPTO Bd of Patent Appeals & Interferences; Patent Trial & Appeal Bd Decs.

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