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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 15/711,316 | 09/21/2017 | Roger SCHIBLI | MERCK-4432-C01 | 9717 |

23599 7590 09/02/2020

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| EXAMINER |
|---|
| DONOHUE, SEAN R |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1618 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 09/02/2020 | ELECTRONIC |

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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*Ex parte* ROGER SCHIBLI, RUDOLF MOSER, CRISTINA MAGDALENA MULLER, SIMON MENSAH AMET AMEY, TOBIAS LUDWIG ROSS, and VIOLA GROEHN

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Appeal 2020-000496
Application 15/711,316
Technology Center 1600

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Before ERIC B. GRIMES, FRANCISCO C. PRATS, and LILAN REN, *Administrative Patent Judges*.

PRATS, *Administrative Patent Judge*.

DECISION ON APPEAL

Pursuant to 35 U.S.C. § 134(a), Appellant[1] appeals from the Examiner's decision to reject claims 1–12 and 15–22. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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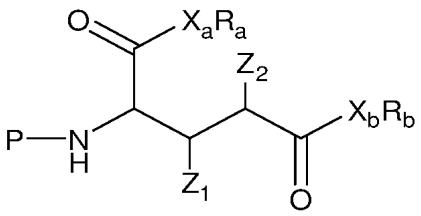
[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies MERCK & CIE, Schaffhausen, Switzerland, as the real party in interest. Appeal Br. 1.

STATEMENT OF THE CASE

Appellant's invention "is directed towards new $^{18}$F-folate radiopharmaceuticals, wherein fluorine-18 is covalently linked to the glutamate portion of a folate or derivative thereof." Spec. 1.

Appellant's claim 1, the sole independent claim on appeal, reads as follows:

1. A compound of formula I,



I

wherein

| | |
|---|---|
| P | is a pteroyl group or a derivative thereof, |
| $X_a$, $X_b$ | are independently of each other C, N, O, or S, |
| $R_a$, $R_b$ | are independently of each other H or straight-chain or branched $C_1$–$C_{12}$ alkyl, $C_3$–$C_6$ cycloalkyl, or $C_5$–$C_{14}$ aryl or $C_5$–$C_{14}$ heteroaryl, which independently of each other are unsubstituted or substituted by at least one CN, Hal, or $NO_2$, and wherein one or more of embedded, non-adjacent $CH_2$ groups may independently be replaced by -O-, -CO-, -CO-O-, -CO-NR'-, -$SO_2$-, -CH=CH-, or -C≡C- |
| R' | is H or $C_1$–$C_6$ alkyl; and |
| $Z_1$, $Z_2$ | are independently of each other H or $^{18}$F, |

*with the proviso that one of $Z_1$ and $Z_2$ is $^{18}$F.*

Appeal Br. 25 (emphasis added).

The following rejections are before us for review:

(1) Claims 1–4, 7–11, 15, 16, and 18 under 35 U.S.C. § 103(a) as being unpatentable over Bettio[2] and Dinkelborg[3] (Ans. 3–5);

(2) Claims 1–12, 15, 16, 18, 21, and 22 under 35 U.S.C. § 103(a) as being unpatentable over Bettio, Dinkelborg, and Coward[4] (Ans. 6–7); and

(3) Claims 1–4, 7–11, and 15–20 under 35 U.S.C. § 103(a) as being unpatentable over Bettio, Dinkelborg, Arstad,[5] and Low[6] (Ans. 7–8).

## DISCUSSION

### *The Examiner's Prima Facie Case*

In rejecting Appellant's claim 1 over Bettio and Dinkelborg, the Examiner cites Bettio as describing $^{18}$F-labeled folate derivatives useful for positron emission tomography (PET) imaging of folate receptor-positive tumors. Ans. 3–5. The Examiner notes in particular that the $^{18}$F-label is attached to the native folate molecule as part of a fluorobenzylamine prosthetic group. *See id.* at 4 (showing compounds 2 and 3 of Bettio).

The Examiner notes that native unlabeled folate, shown as compound 1 in Bettio's Figure 1, "reads in part" on a compound of formula I of Appellant's claim 1. Ans. 4. In particular, the Examiner finds that the native unlabeled folate taught in Bettio differs from the compound of

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[2] Andrea Bettio et al., *Synthesis and Preclinical Evaluation of a Folic Acid Derivative Labeled with $^{18}$F for PET Imaging of Folate Receptor-Positive Tumors*, 47 J. NUCL. MED. 1153–1160 (2006).
[3] CA 2 667 395 A1 (published May 8, 2008).
[4] US 4,628,090 (issued Dec. 9, 1986).
[5] WO 2006/067376 A2 (published June 29, 2006).
[6] WO 2006/071754 A2 (published July 6, 2006).

Appellant's claim 1 in that Bettio "do[es] not teach a folate derivative of the instant claims where at least one of $Z_1$ or $Z_2$ is $^{18}F$." *Id.* at 5.

The Examiner cites Dinkelborg as evidence that the compound of Appellant's claim 1 would have been obvious despite the differences between the claimed compound and the native unlabeled folate taught in Bettio. Ans. 5. Specifically, the Examiner cites Dinkelborg as describing the preparation of $^{18}F$-labeled glutamate derivatives, in which the $^{18}F$ is present at the position corresponding to the position of the $^{18}F$ recited in Appellant's claim 1. *Id.*

Based on the references' combined teachings, the Examiner concludes that it would have been obvious to "modify the native folic acid taught by Bettio et al. by incorporating $^{18}F$ at the folic acid moiety as taught by Dinkelborg et al. because it would advantageously enable minimum deviation from its native structure without the [need] for a prosthetic group." Ans. 5. In addition, the Examiner reasons, it would have been obvious to "detect cells overexpressing the folate receptor in vitro as taught by Dinkelborg et al. because it would advantageously enable comparison with a gold standard oncological investigations." *Id.*

*Analysis*

As stated in *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a *prima facie* case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), although the Supreme Court emphasized "an expansive and flexible approach" when evaluating claims for obviousness, *id.* at 415, the Court nonetheless also reaffirmed the importance of determining "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 418.

Consistent with the flexible approach emphasized in *KSR*, our reviewing court has explained that, in cases involving claims to new chemical compounds, "it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

In other words, establishing that a chemical compound would have been obvious requires "a showing that the prior art would have suggested making *the specific molecular modifications* necessary to achieve the claimed invention." *Takeda*, 492 F.3d at 1356 (emphasis added; internal quotations omitted). *See also Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1374 n.3 (Fed. Cir. 2008) (Even post-*KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.").

In the present case, having carefully considered all of the arguments and evidence advanced by the Examiner and Appellant, Appellant persuades us that the Examiner has not explained with sufficient specificity why the combined teachings of Bettio and Dinkelborg would have suggested

preparing a folate derivative having an $^{18}F$ atom at one of the specific positions required by Appellant's claim 1. We acknowledge, as the Examiner contends, that folate includes a glutamate moiety within its structure. *See* Ans. 9 ("The folate in Bettio is not structurally unrelated to the glutamate in Dinkelborg because folate comprises glutamate."). The mere fact that folate might not be unrelated to glutamate does not persuade us, however, that a skilled artisan would have been motivated to apply, to folate, Dinkelborg's teachings regarding $^{18}F$ fluorination of glutamate. As Appellant points out, the overall structure of native folate differs significantly from the glutamate derivatives described in Dinkelborg as being derivatized with $^{18}F$ atoms. *Compare* Bettio 1154 (compound 1 of Bettio's Figure 1 showing native folate) *to* Dinkelborg 28–31 (showing structures of glutamate derivatives $^{18}F$-fluorinated in Dinkelborg's Schemes 1–3).

Given the significant differences between the structure of native folate and the structures of the glutamate derivatives described in Dinkelborg as being derivatized with $^{18}F$ atoms, we agree with Appellant that, absent improper hindsight gleaned from Appellant's disclosure, a skilled artisan would not have considered native folate to be interchangeable with glutamate in Dinkelborg's $^{18}F$-fluorination process. We therefore also agree with Appellant that the Examiner has not explained sufficiently why the combined teachings of Bettio and Dinkelborg would have suggested preparing the specific compound recited in Appellant's claim 1.

We acknowledge, as the Examiner contends, that claim 1 is directed to a compound, rather than a method of synthesizing the compound. *See* Ans. 8; *see also id.* at 10 ("[T]here are no method of synthesis claims under

rejection."). Our reviewing court's predecessor has explained, however, that "if the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public." *In re Hoeksema*, 399 F.2d 269, 274 (CCPA 1968); *see also In re Payne*, 606 F.2d 303, 314 (CCPA 1979) ("References relied upon to support a rejection under 35 USC § 103 must provide an enabling disclosure, [i]. e., they must place the claimed invention in the possession of the public. . . . *An invention is not possessed absent some known or obvious way to make it*.") (emphasis added; citation and internal quotations omitted).

In the present case, given the significant differences between the structure of native folate and the structures of the glutamate derivatives described in Dinkelborg as being derivatized with $^{18}F$ atoms, we are not persuaded that the Examiner has explained with sufficient specificity how the combined teachings of Bettio and Dinkelborg would have provided a known or obvious way to make the compound of Appellant's claim 1. As to that issue, the Examiner argues as follows:

> Bettio teaches that an unprotected folate, which includes an unprotected pteroate, can be coupled to 4-[$^{18}F$]fluorobenzylamine in only 30 min. On pg. 1154, Bettio states that a DMSO solution containing folic acid was added to the reaction vial and the coupling was formed by heating at 100°C for 30 min. On pg. 29, Dinkelborg teaches a 2 step radiosynthesis of 4-[$^{18}F$]fluoroglutamic acid when starting from a nickel complex and pg. 31, Dinkelborg teaches the 1 step radiosynthesis of protected 4-[$^{18}F$]fluoroglutamic acid without a Ni complex. A person of ordinary skill in the art would have been motivated to couple the 4-[$^{18}F$]fluoroglutamate derivative in Dinkelborg to an activated pterote, which Bettio suggests can be done in 30 min, in order to gain the following advantages: (i)

> reduced number of impractical to separate regioisomers (greater purity), and (ii) $^{18}$F-labeled derivative with minimal structural deviation from native folate. Appellants have not provided any evidence that the claimed $^{18}$F-labelled compounds were not enabled prior to the instant invention.

Ans. 10–11.

We are not persuaded. The Examiner does not explain, specifically, how Bettio's teaching of coupling a fluorobenzylamine to an unprotected folate suggests that a skilled artisan would have been able to perform the distinct reaction posited by the Examiner, coupling Dinkelborg's fluoroglutamate to a pteroate moiety. Nor does the Examiner support this alternative rationale by identifying persuasive evidence suggesting that, rather than following Bettio's teaching of coupling a fluorobenzylamine to an unprotected folate, a skilled artisan would have been motivated instead to perform a different reaction, the coupling of Dinkelborg's fluoroglutamate to a pteroate moiety.

We acknowledge, as the Examiner contends, that Appellant may rebut the Examiner's prima facie case by advancing evidence that the prior art did not enable preparation of the claimed compound. *See* Ans. 11. The Examiner, however, bears the initial burden of providing an evidentiary basis to support a conclusion of obviousness. *See In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992) ("[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.").

In the present case, while we acknowledge the teachings in Bettio and Dinkelborg identified by the Examiner, we are not persuaded that the Examiner has explained with sufficient specificity why, absent improper

hindsight, those teachings suggest the specific compound recited in Appellant's claim 1. Nor are we persuaded that the Examiner has explained, with sufficient specificity, why the identified teachings in Bettio and Dinkelborg establish that a skilled artisan would have been able to make the compound of Appellant's claim 1. We therefore reverse the Examiner's rejection of claim 1, and its dependent claims, for obviousness over Bettio and Dinkelborg.

In rejecting claim 1 over Bettio, Dinkelborg, and Coward, the Examiner relies on teachings in Bettio and Dinkelborg cited in the rejection discussed above, and additionally cites Coward "as discussed above." Ans. 6. While the Examiner's Answer does not previously mention Coward, the Examiner's Answer later cites Coward as teaching "folate analogs of the instant formulas and there is a clear teaching and suggestion to place a fluorine on the glutamate of the folate derivatives therein." Ans. 9–10 (citing Coward 13:10–19 (claim 1)). Based on this teaching, the Examiner reasons as follows:

> The addition of fluorine to glutamate of a folate derivative can be readily gleaned from Coward, prior art, and not hindsight reconstruction. The substitution of one H on the glutamate of folate with F reduces the structural deviation folate in comparison to the fluorinated derivatives in Bettio because said substitution merely replaces one atom for another (H for F; Dinkelborg and Coward) in contrast to replacing an α- or γ-carboxyl OH with a 4-fluorobenzylamine (Bettio).

*Id.* at 10; *see also id.* at 12 ("Coward was relied on for teaching the replacement of a glutamate moiety of a folate derivative with a 4-fluoroglutamate. Bettio and Dinkelborg teach methods of $^{18}$F-labeling.").

We find that the Examiner's citation of Coward does not remedy the deficiencies of the combination of Bettio and Dinkelborg, discussed above,

in relation to Appellant's claim 1. In particular, even acknowledging that Coward's methotrexate includes a glutamate moiety within its structure, we are not persuaded that the Examiner has identified any specific teachings in Coward that explain sufficiently why a skilled artisan would have prepared the compound of Appellant's claim 1, when combined with Bettio and Dinkelborg. While the Examiner asserts that addition of a fluorine to glutamate of a folate derivative "can be readily gleaned from Coward" (Ans. 10), the Examiner does not point to any specific teaching in support of that assertion, nor does the Examiner explain, specifically, why Coward would have led a skilled artisan to that conclusion.

Similarly, while the Examiner asserts that a skilled artisan "could have combined the publications[']description of the invention with his or her own knowledge to make the claimed invention" (Ans. 12 (citing MPEP § 2121.01)), we are not persuaded that the Examiner has explained with adequate specificity *why* a skilled artisan could have, or even would have, combined the cited teachings in the prior art in the manner required to arrive at the compound recited in Appellant's claim 1. Because we are not persuaded that the Examiner has explained, with sufficient specificity, why Bettio, Dinkelborg, and Coward would have suggested preparing the compound of Appellant's claim 1, we reverse the Examiner's rejection of claim 1, and its dependent claims, for obviousness over Bettio, Dinkelborg, and Coward.

In rejecting Appellant's claims 1–4, 7–11, and 15–20 over Bettio, Dinkelborg, Arstad, and Low, the Examiner relied on Arstad and Low as evidence that it would have been obvious to use an $^{18}$F-labeled folate derivative in diagnostic processes recited in Appellant's claims 15–20,

which depend from claim 1, discussed above. *See* Ans. 7–8. Accordingly, because the Examiner does not identify, nor do we discern, any specific teachings in Arstad and Low that remedy the deficiencies in the combination of Bettio and Dinkelborg discussed above in relation to claim 1, we also reverse the Examiner's rejection of claims 1–4, 7–11, and 15–20 over Bettio, Dinkelborg, Arstad, and Low.

DECISION SUMMARY

In summary:

| **Claims Rejected** | **35 U.S.C. §** | **Reference(s)/Basis** | **Affirmed** | **Reversed** |
|---|---|---|---|---|
| 1–4, 7–11, 15, 16, 18 | 103(a) | Bettio, Dinkelborg | | 1–4, 7–11, 15, 16, 18 |
| 1–12, 15, 16, 18, 21, 22 | 103(a) | Bettio, Dinkelborg, Coward | | 1–12, 15, 16, 18, 21, 22 |
| 1–4, 7–11, 15–20 | 103(a) | Bettio, Dinkelborg, Arstad, Low | | 1–4, 7–11, 15–20 |
| **Overall Outcome** | | | | 1–12, 15–22 |

REVERSED