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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a compound and pharmaceutical preparation of central nicotine receptor subtype agonists, which may be used for conditions or treatments such as Alzheimer’s disease and smoke substitution therapy. (Spec., 9–10.) We have jurisdiction under 35 U.S.C. § 6(b).

We affirm.
STATEMENT OF THE CASE

Claims on Appeal

Claims 20, 26, and 27 are on appeal. Claim 20 is illustrative and reads as follows:

20. (−)[3aR-(3aa, 8ba)]-1,2,3,3a,4,8b-Hexahydropyrrolo-
[3′,2′:4,5]cycloptenta[1,2-c]pyridine dihydrochloride or a pharmaceutically usable salt thereof.

(Br. 7, Claims Appendix.)

Examiner’s Rejections

A. Claims 20 and 26 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Zhai, 1 Patani, 2 and Ullrich. 3 (Ans. 5.)

B. Claim 27 stands rejected under 35 U.S.C. § 103(a) as unpatentable over Zhai, Patani, Ullrich, and Le. 4 (Ans. 9.)

Appellants have presented arguments for the patentability of claims 20 and 26 as a group. (Br. 1–5.) Therefore, we limit our discussion to claim 20 as representative of both claims 20 and 26.

FINDINGS OF FACT

FF 1. The Examiner finds that Zhai teaches a compound named cis-l-methyl-1,2,3,3a,8b-hexahydroxyprrolo[3,2-f]pyridine, with a conformation rigidified by a methylene bridge, and the following structure:

1 Zhai et al., A Facile Synthesis of cis-l-Methyl-1,2,3,3a,4,8b-
hexahydropyrrolo[3,2-f]pyridine, an Annulated Nicotine Analog, 4
2 G.A. Patani & E.J. LaVoie, Bioisosterism: A Rational Approach in Drug
3 Ullrich et al., Conformationally Constrained Nicotines: Polycyclic,
Bridged, and Spiro-Annulated Analogues as Novel Ligands for the Nicotinic
Acetylcholine Receptor, 45 J. MED. CHEM. 4047–54 (2002).
FF 2. The Examiner finds that Zhai’s teachings show that its compound (FF 1) has the ability to target and activate nicotinic acetylcholine receptors (nAChRs) and has favorable effects on patients with Alzheimer’s disease. (Id.)

FF 3. The Examiner finds that the structure of the elected compound (claim 20) is as follows:

(Ans. 6–7.)

FF 4. The Examiner finds that a difference between the Zhai compound and the claimed compound is that the pyrrolo group has a methyl group (Me) on the Zhai compound (FF 1) whereas the claimed compound contains hydrogen in place of the methyl group (FF 3). (Id.)

FF 5. Patani states that “[b]ioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents.” (Patani, p. 3147.)

FF 6. The Examiner finds, based on the teachings of Patani, that the Zhai
compound and the elected compound (claim 20) are bioisosteres of each other, and that “[h]ydrogen is a bioisostere replacement for methyl (Grimm’s Hydride Displacement Law).” (Ans. 7; Patani p. 3152.)

FF 7. The Examiner finds that Ullrich teaches that conformation restraint of nicotine-related compounds can lead to high affinity ligands, which are stereochemically discriminated by nAChRs. (Ans. 8.)

FF 8. Ullrich states that nAChRs are “a potential target for the treatment of Alzheimer’s and other neurodegenerative diseases.” (Ullrich, p. 4047.)

FF 9. Le states that compositions of its invention can be used for treatment of Alzheimer’s disease, and “can be used in combination therapies with opioids and other analgesics,” including numerous ones listed in Le. (Le, ¶¶ 73, 80.)

ISSUE

Whether a preponderance of evidence of record supports the Examiner’s conclusion of obviousness with respect to claim 20.

Analysis

The Examiner determined that claim 20 would have been obvious to a person of ordinary skill in the art. (Ans. 5–9.) This determination was based, in part, on the finding that the structural difference between the compound of claim 20 and the Zhai compound is the replacement of the methyl group on the Zhai compound with hydrogen, and the teaching of Patani that hydrogen is a bioisostere replacement for methyl. (FF 4, 6.) Furthermore, the Examiner found that Ullrich teaches that conformation restraint of nicotine-related compounds can lead to high affinity ligands. (FF 7.) Finally, the Examiner set forth motivation from the prior art to
combine the teachings of Zhai, Patani, and Ullrich, with a reasonable expectation of success. (Ans. 8–9.)

We find that the Examiner has established a prima facie case of obviousness. See Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (“In the chemical arts, . . . ‘structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness’”) (citing cases). Furthermore, as discussed below, we find that Appellants’ arguments do not overcome or rebut that prima facie case.

Bioisosterism in Nicotine-Like Compounds

Appellants contend that N-methyl is not bioisosteric with N-hydrogen in nicotine-like compounds, and set forth several arguments in support of that contention. (Br. 2–4.)

First, Appellants argue that Patani shows that N-methyl and N-hydrogen are not bioisosteric in the context of nicotine-like compounds, citing a statement in Patani that, according to Appellants, indicates that N-methyl and N-hydrogen are not bioisosteric in every context. (Id. at 2.) Appellants also point to data in Patani (Table 12) as showing that a “hydrogen substituted compound was about 6 times less active” than a methyl substituted compound. (Id. at 2–3.) According to Appellants, Patani thus demonstrates that methyl and hydrogen cannot be exchanged “without significantly changing the activity of the compound.” (Id. at 2.)

Second, Appellants cite to Ullrich for the proposition that “[i]ntroduction of the N-methyl substituent resulted in a significant improvement” and “[i]n the case of [compound (+)-5b]. . . the beneficial
effects of an N-methyl group . . . were demonstrated.” (Id. at 3, citing Ullrich, p. 4050.)

Appellants buttress their first and second arguments with the Ullrich Declaration, which states that “in compounds such as 5b, an N-methyl group is superior to the N-unsubstituted analog in terms of binding affinity” and “in the context of nicotine-like compounds, the N-methyl group is not bioisosteric with N-hydrogen.” (Id., citing Ullrich Dec. ¶ 4.) Appellants conclude by stating that Patani and Ullrich “generally indicate that replacing the N-methyl with N-hydrogen is detrimental to a nicotine-like compound’s activity” and, as such, those references teach away from the claimed compounds. (Id. at 4.)

We are not persuaded by Appellants’ arguments. Patani teaches hydrogen and methyl are bioisosteres, thereby suggesting that their substitution would result in the same type of biological activity. (FF 6.) See In re Merck & Co., Inc., 800 F.2d 1091, 1096 (Fed. Cir. 1986) (describing bioisosterism). Furthermore, while Table 12 of Patani shows that a hydrogen substituted compound was less active than a methyl substituted compound in inhibiting a particular enzyme, Patani also shows that hydrogen and methyl are bioisosteres and that the hydrogen substituted compound retained activity. (Patani, p. 3153.)

Appellants essentially argue that Patani shows that substituting hydrogen in place of a methyl group may result in a compound that is less active. (Br. 2–3.) However, “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a

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5 Declaration of Dr. Thomas Ullrich under 37 C.F.R. § 1.132, dated Sept. 26, 2011.
reasonable probability of success.” Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). As such, the mere difference in the degree of activity, resulting from substitution of the bioisosteres hydrogen and methyl in certain contexts, does not overcome the prima facie case of obviousness.

Appellants’ argument regarding the Ullrich reference, as buttressed by the Ullrich Declaration, is unpersuasive for several reasons. Appellants’ argument is that the N-hydrogen substitution is inferior to N-methyl. (Br. 3.) However, as pointed out by the Examiner, the Ullrich compounds referenced by Appellants (5a, 5b) are structurally dissimilar from the Zhai compound and the claimed compound. (Ans. 15–16.) Moreover, simply because Ullrich may describe an N-hydrogen compound as somewhat inferior to an N-methyl compound does not make an N-hydrogen compound patentable. See In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Appellants’ argument that Patani and Ullrich teach away from the claimed compound is likewise unpersuasive. Ullrich shows that an N-hydrogen compound can have better activity than an N-methyl compound. (Ans. 16; Ullrich, p. 4050.) Patani shows that hydrogen and methyl are bioisosteres (FF 6), and that hydrogen substitution retains enzyme inhibition activity. (Patani, pp. 3152–53.) Thus, neither Ullrich nor Patani can be said to teach away because they do not “criticize, discredit, or otherwise discourage” the claimed solution of substituting the N-methyl in Zhai with hydrogen. See In re Fulton, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Separation of Enantiomers

Appellants contend that, based on the teachings of Ullrich, a person of ordinary skill in the art would not have been motivated to separate the enantiomers of Zhai’s compound. (Br. 4.) Furthermore, according to
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Appellants, there would have been no “reasonable expectation of success that the enantiomers would have any ‘remarkable enantioselectivity,’” as this was not observed with all of the compounds Ullrich tested.” (Id., citing Ullrich, p. 4050.) Appellants also cite to the Ullrich Declaration and the statements therein that the Ullrich reference shows that “conformational restriction . . . does not necessarily lead to an increase of enantioselectivity” and that the Ullrich reference “does not teach any predictivity of receptor stereoselectivity based on conformational restriction.” (Br. 4–5; Ullrich Dec., ¶ 7.)

We are not persuaded by Appellants’ argument that enantioselectivity cannot be predicted. As stated above, obviousness is not overcome by merely showing some degree of unpredictability in the art. Pfizer, 480 F.3d at 1364. Moreover, Ullrich shows, and the Ullrich Declaration confirms, the enantioselectivity of certain compounds (5a, 5b), and that one enantiomer is generally expected to have better activity in a given assay compared to the other enantiomer. (Ans. 18–19; Ullrich, p. 4050; Ullrich Dec., ¶ 7.)

Unexpected Results

Appellants also argue that, even if the Examiner established a prima facie case of obviousness, the claimed compound “possesses unexpectedly advantageous or superior properties.” (Br. 5.) Appellants point to Example 9 in the Specification as demonstrating “a remarkable difference” in the properties between the claimed compound and its enantiomer. (Id.) This argument is also buttressed with the statement in the Ullrich Declaration that he “would not have expected such high enantioselectivity as reported in Example 9.” (Id.; Ullrich Dec. ¶ 8.)
We are not persuaded by Appellants’ argument. Unexpected results must be shown to be unexpected compared with the closest prior art. In re Baxter Travenol Labs, 952 F.2d 388, 392 (Fed. Cir. 1991) (citing In re De Blauwe, 736 F.2d 699, 705 (Fed. Cir. 1984)). In this case, the closest prior art is the Zhai compound. Moreover, a difference in properties between the enantiomers of Example 9 would not have been unexpected or surprising to a person of ordinary skill in the art given the teachings of the Ullrich reference. See In re Soni, 54 F.3d 746, 750–751 (Fed. Cir. 1995).

CONCLUSION OF LAW

A preponderance of evidence of record supports the Examiner’s conclusion that claim 20 is obvious under 35 U.S.C. § 103(a). Furthermore, Appellants have not provided sufficient evidence of unexpected results that, when weighed with the evidence favoring obviousness, shows that the claimed compound would have been nonobvious.

Claim 26 was not argued separately and therefore falls with claim 20. 37 C.F.R. § 41.37(c)(1)(iv).

ISSUE

Whether a preponderance of evidence of record supports the Examiner’s conclusion of obviousness with respect to claim 27.

Analysis

Claim 27 recites “[t]he pharmaceutical preparation of claim 26, further comprising an additional therapeutically valuable compound.” (Br. 7.) The Examiner found that it would have been obvious to combine the additional therapeutically valuable compound of Le, in view of the prior art, with the expectation of a better action for improving Alzheimer’s disease, and to test and check such action. (Ans. 10.) Appellants argue that
“there is no teaching or suggestion of the expectation that such additional compounds may be successfully employed with the currently claimed compound, nor could there be.” (Br. 6.)

We are not persuaded by Appellants’ argument. “It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose.” *In re Kerkhoven*, 626 F.2d 846, 850 (CCPA 1980) (citing cases). Here, the Le composition is useful for treating Alzheimer’s (FF 9), and it would have been obvious to combine it with a pharmaceutical preparation for treating Alzheimer’s as taught by the prior art (e.g. claim 26). *See id.* Accordingly, we find that the Examiner has established a prima facie case of obviousness as to claim 27, and Appellants have not presented sufficient evidence and argument in rebuttal to overcome that prima facie case.

**CONCLUSION OF LAW**

A preponderance of evidence of record supports the Examiner’s conclusion that claim 27 is obvious under 35 U.S.C. § 103(a).

**SUMMARY**

We affirm the rejection of all appealed claims.

**TIME PERIOD FOR RESPONSE**

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

**AFFIRMED**