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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte LIN CHENG and JENNIFER RIGGS-SAUTHIER

Appeal 2018-000608
Application 13/995,415
Technology Center 1600

Before RICHARD M. LEBOVITZ, ULRIKE W. JENKS, and TAWEN CHANG, *Administrative Patent Judges*.

CHANG, *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, 10, and 16. We have jurisdiction under 35 U.S.C. § 6(b).

We REVERSE.

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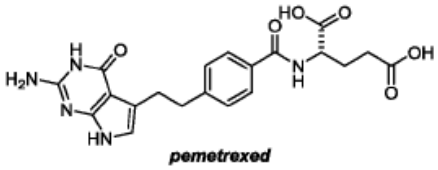
[1] We use the word "Appellant" to refer to "applicant" as defined in 37 C.F.R. § 1.42. Appellant identifies the real party in interest as Nektar Therapeutics. Appeal Br. 3.

BACKGROUND

Pemetrexed, an antifolate drug, has been used to treat cancer patients and has the following chemical structure:

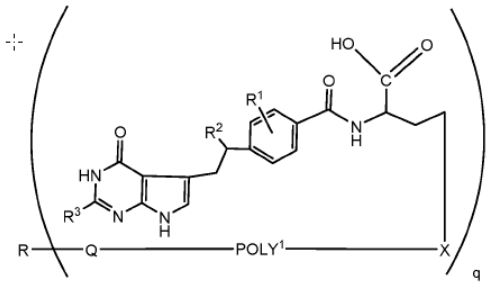


Spec. ¶ 5; Ans. 13. The Specification states that it would be desirable to modify pemetrexed in order to "(i) reduce peak-to-trough variation (with the potential to reduce dose-limiting toxicities), (ii) accumulate in tumor tissues while still retaining efficacy, and (iii) extend the effective half-life to thereby provide less frequent dosing." *Id.* ¶ 8. The invention "seeks to address these and/or other needs" by providing certain pemetrexed conjugates. *Id.* ¶ 9.

CLAIMED SUBJECT MATTER

The claims are directed to a conjugate of pemetrexed according to a recited formula. Claim 1 is illustrative:

1. A conjugate according to Formula I:



Formula I

wherein:

R is a residue of pentaerythritol;

R^1 is H;

R^2 is H;

R^3 is amino;

Q is -O-;

$POLY^1$ is a poly(alkylene glycol);

X is $-C(O)-NHCH_2CH_2(OCH_2CH_2)_2NH-C(O)-$, $-CH_2-C(O)-NHCH_2CH_2OCH_2CH_2O-C(O)-$, or $-CH_2-C(O)-NH-CH_2-CH(R^4)-O-C(O)-$;

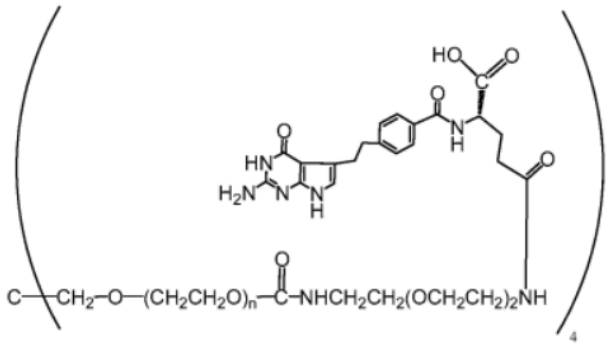
R^4 is H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$, or $-CH(CH_3)CH_2CH_3$; and

q is 4;

and pharmaceutically acceptable salts and solvates thereof.

Appeal Br. 12 (Claims App.).

In response to the Examiner's September 28, 2015 Requirement for Restriction/Election, Appellant elected without traverse compound 20d, which has the structure set forth below:



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wherein n is defined to provide a 4-arm-PEG 40k. Reply to Restriction Requirement (Nov. 24, 2015). We limit our consideration on the merits to the elected species. *See Ex parte Ohsaka*, 2 USPQ2d 1460, 1461 (BPAI 1987).

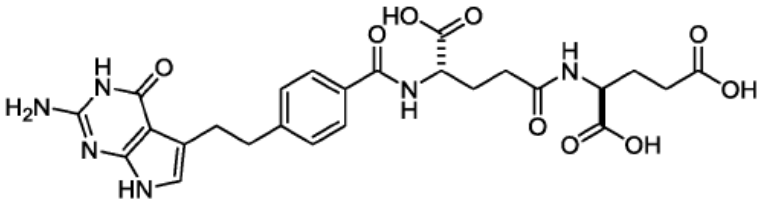
REJECTION(S)

A. Claims 1, 10, and 16[2] are rejected under pre-AIA 35 U.S.C. § 103(a) as being unpatentable over Ootsu,[3] Harris,[4] and Zhao.[5]

OPINION

A. Issue

The Examiner finds that Ootsu teaches "oligoglutamate conjugates of folates (i.e. oligomeric conjugates . . .) including pemetrexed derivatives like the amide-linked one shown below":



Ans. 3. The Examiner finds that Ootsu further discloses that "oligo-conjugates are excellent anti-tumor compounds with highly specific toxicities for cancers, and have excellent water solubility." *Id.* at 4.

The Examiner finds that Ootsu "does not specifically disclose the . . . claimed polymer scaffold." *Id.* However, the Examiner finds that Harris teaches "improved drug-polymer multifunctional conjugates based on, for example, pegylated pentaerythritol . . . that are useful with drugs such as

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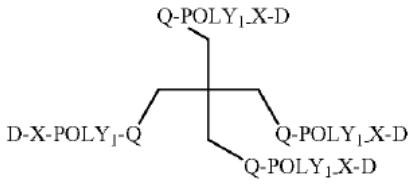
[2] Claims 4–7 and 15 have been withdrawn. Appeal Br. 4.
[3] Akimoto et al., EP 0 492 316 A1, published July 1, 1992. Although Akimoto is listed as the first inventor, both the Examiner and Appellant refers to the reference as Ootsu. Thus, to avoid confusion, we also refer to the reference as Ootsu in our opinion.
[4] Harris et al., US 2006/0275252 A1, published Dec. 7, 2006.
[5] Zhao et al., US 2009/0074704 A1, published Mar. 19, 2009.

pemetrexed" and that Zhao teaches "multi-arm polymeric prodrugs . . . based on the pentaerythritol-scaffold shown below":



Id. The Examiner finds that Zhao exemplifies this class of drugs with different anti-cancer compounds, thus demonstrating that "the polymer-conjugates can be beneficially used with different anti-cancer drugs with unrelated structural motifs." *Id.* The Examiner also finds that Zhao teaches that "X in Q-POLY$_1$X-D can preferably be - $(CR_xR_y)_a$-K-$(CR_xR_y)_b$-$(OCH_2CH_2)_c$-Z where $R_{[x]}$ and $R_{[y]}$ can be H, a can be 0, K can be –C(O)NH-, c can be 2, and Z can be a variety of carbonyl functionalities . . . ; i.e. X can preferably be -C(O)NH-$(CH_2)_2$-$(OCH_2CH_2)_{[2]}$-carbonyl linker." *Id.* at 5. In short, the Examiner cites Harris for suggesting conjugating pemetrexed with a multi-arm PEG polymer, as claimed, and cites Zhao for suggesting a multi-arm PEG polymer conjugate with the specific claimed spacer between the PEG polymer and active ingredient.

The Examiner finds that a skilled artisan "would have been motivated to make and use pemetrexed conjugated via an amide to a multi-arm polymer," with a reasonable expectation of success, because "the prior art demonstrates that pemetrexed can be beneficially modified via conjugation, discloses an appropriate site on pemetrexed for attachment, discloses the attachment via an amide linkage, and teaches that pemetrexed can be beneficially conjugated to a multi-arm PEG-based polymer." *Id.* at 5. The Examiner further finds that a skilled artisan "would have been motivated to

make and use pemetrexed conjugated with the claimed species of polymer," with a reasonable expectation of success, because "the prior art demonstrates that the claimed class of polymer-conjugates are useful for the treatment of cancers, demonstrates that different cancer compounds can be successfully appended to the class of polymer conjugates, and teaches which portions of the conjugate can, and should, be modified and in what fashion." *Id.* at 5–6. The Examiner notes that "compounds differing by the successive addition of the same chemical group, e.g., by -CH2- groups or PEG groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties," and, "[a]bsent any criticality, the simple addition or deletion of repeat groups would be *prima facie* obvious." *Id.*

Appellant contends that the combination of prior art would not result in a conjugate within the scope of claim 1. Appeal Br. 9–10.

Appellant further contends that "a finding of obviousness based on chemical similarity requires . . . (i) the selection of a lead compound, (ii) identification of a reason to modify the lead compound, and (iii) the predictability of the result of the modification to the lead compound." *Id.* at 7–8. Appellant contends the Examiner has not explained why a skilled artisan would have selected any particular compound in Ootsu as a lead compound for modification or why a skilled artisan would have modified such a compound to arrive at the claimed invention. *Id.* at 8. Appellant contends that, in fact, a skilled artisan "looking to optimize the conjugates of Ootsu would have retained the oligoglutamate moiety of these compounds, since it is these moieties which are asserted in Ootsu to provide beneficial properties." *Id.* Appellant further contends that a skilled artisan "would

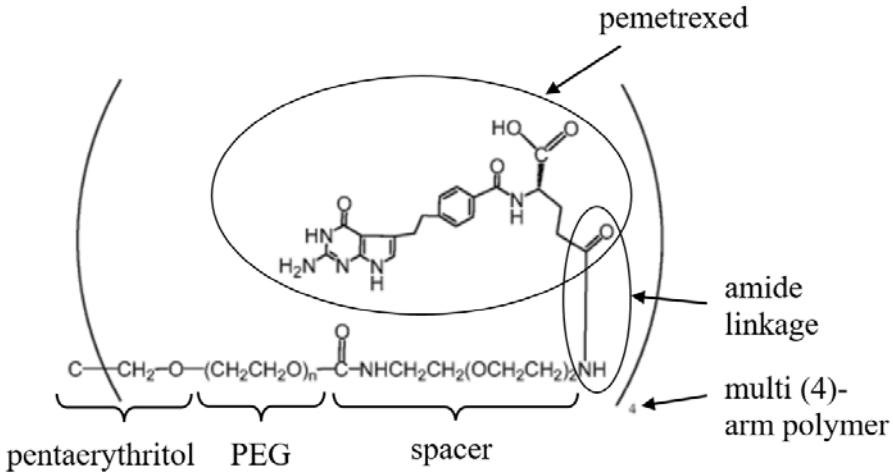
[not] have had a reasonable expectation of success or predictable results in making and testing a hypothetical pemetrexed conjugate" because Zhao "show[s] significantly different efficacy for conjugates of anti-cancer drugs with unrelated structural motifs." *Id.* at 8–9.

Finally, Appellant contends that the claimed subject matter exhibits unexpected results. *Id.* at 7.

The issue with respect to this rejection is whether a skilled artisan would have had reason to combine the teachings of the cited prior art to arrive at the elected compound, with a reasonable expectation of success.

B. Analysis

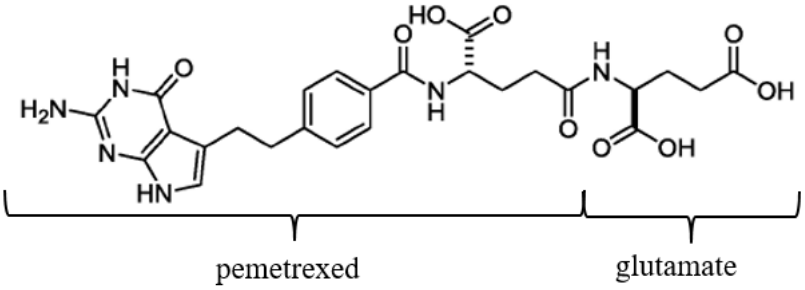
To facilitate our discussion, the elected species is reproduced below with annotations:



On balance, we find Appellant to have the better argument. In particular, the Examiner has not persuasively explained why a skilled artisan, in view of Ootsu, Harris, and Zhao, would have had reason to conjugate pemetrexed to the multi-arm polymer suggested by Zhao

(corresponding to the claimed pentaerythritol, PEG, spacer) *via an amide linkage*, as required by the elected species of the claims.

The Examiner asserts that Ootsu teaches that the amide-linked pemetrexed derivative shown below is an excellent anti-tumor compound that also has excellent water solubility:



Ans. 3–4 (annotations added). The Examiner asserts the prior art suggests anti-cancer drugs including pemetrexed can be beneficially conjugated to the claimed multi-arm PEG-based polymer, while this disclosure in Ootsu teaches both "an appropriate site on pemetrexed for attachment" as well as "attachment via an amide linkage." *Id.* at 5. The Examiner asserts that, given the combination of these disclosures, a skilled artisan would have had reason to "attach pemetrexed with an amide linker to a multi-arm PEG-based polymer during the routine optimization of pemetrexed derivatives," with a reasonable expectation of success. *Id.* at 5–6.

We are not persuaded. Ootsu teaches that certain condensed heterocyclic oligoglutamate derivatives, including the glutamate derivative of pemetrexed, are useful as water-soluble antitumor agents. Ootsu Title, Abstract, 2:3–4, 4:4–11, 9:17–18, claim 29. The Examiner essentially suggests that it would be obvious to a skilled artisan to replace the glutamate moiety of the compound taught in Ootsu with the multi-arm polymer

conjugate taught by Zhao, while retaining the amide linkage of Ootsu's compound.[6]

As an initial matter, the Examiner does not persuasively explain why a skilled artisan would replace the glutamate moiety of Ootsu's compound, given that Ootsu teaches that glutamate moieties provide beneficial properties to the compound.

In response to that argument by the Appellant, the Examiner states that, while "[t]he disclosure of Ootsu . . . generally teaches that oligoglutamate compounds have beneficial properties with respect to the parent, non-oligomer conjugated, compounds," it is "silent as to the benefit, or lack thereof, of alternate oligomer-conjugation," and such "silence is not sufficient to be a teaching-away from the use of alternate oligomers for conjugation." Ans. 11.

We agree that Ootsu does not teach away from the use of other pemetrexed conjugates. Nevertheless, a lack of teaching away is not the same as a reason to combine, and the Examiner's response does not explain why a skilled artisan would replace the glutamate moiety from Ootsu's compound with Zhao's multi-arm polymer *while retaining an amide linkage between pemetrexed and a different conjugate*.[7] For instance, the Examiner

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[6] The amide linkage in the pemetrexed derivate taught by Ootsu results from the reaction between the terminal carboxylic acid group of the pemetrexed and the amine moiety of the glutamate. That is, the nitrogen in the amide linkage is contributed by the glutamate, not pemetrexed.

[7] In this regard, we note that the Examiner does not suggest that Zhao itself discloses a 4-arm moiety that, when conjugated to pemetrexed, would result in a linkage via an amide bond. The Examiner does not describe how such linkage would be made, e.g., by identifying an amino group in Zhao's polymer through which the conjugation to pemetrexed would be made.

has cited no evidence that it is the amide linkage, rather than the glutamate moiety, that provides the beneficial properties to the pemetrexed derivative taught in Ootsu. Neither has the Examiner provided evidence that the glutamate moiety in Ootsu is functionally equivalent to the multi-arm polymer conjugate of Zhao.

Indeed, we note that Zhao teaches that its polymer conjugate should be attached to the active agent (e.g., pemetrexed) via a hydrolyzable linkage. Zhao ¶ 17. Zhao further teaches that a "hydrolyzable" bond is a bond, such as a carboxylate ester, that "reacts with water (i.e., is hydrolyzed) under physiological conditions," while amides are examples of a hydrolytically stable bond that "does not undergo hydrolysis under physiological conditions to any appreciable extent over an extended period of time." *Id.* ¶¶ 118, 120. If anything, therefore, Zhao would appear to teach away from using an amide linkage with its polymer conjugate unless it forms a linkage that is hydrolytically degradable when taken together with the spacer or a portion of the spacer. *Id.* ¶ 118 (explaining that Z, the linkage to the active agent itself, need not be hydrolytically degradable, if it forms a hydrolytically degradable linkage when taken together with a covalently attached spacer fragment or a portion thereof).

Neither are we persuaded by the Examiner's assertion that a skilled artisan would have "made and used the instantly claimed polymer conjugate of pemetrexed during the routine optimization of the polymer conjugated pemetrexed." Ans. 6. It is true that, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). In this case, however, the Examiner has not

established that the general conditions of the claims are disclosed in the prior art.

Finally, the Examiner argues that

> compounds differing by the successive addition of the same chemical group, e.g., by -CH2- groups or PEG groups, are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. *In re Wilder*, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Absent any criticality, the simple addition or deletion of repeat groups would be *prima facie* obvious.

Ans. 6. We are not persuaded. The Examiner does not explain how the doctrine elucidated in *In re Wilder* applies in this case. "[R]ejections 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." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Accordingly, for the reasons explained above, we reverse the Examiner's rejection of claims 1, 10, and 16 as obvious over Ootsu, Harris, and Zhao.

CONCLUSION

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
1, 10, 16	103(a)	Ootsu, Harris, Zhao		1, 10, 16

REVERSED