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Techfields Pharma Co., Ltd.
2358 Chang'an Road, Building #14, Wujiang District
Suzhou, Jiangsu, 215200
CHINA

EXAMINER

RODRIGUEZ, RAYNA B

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte CHONGXI YU and LINA XU ¹

Appeal 2019-001126
Application 14/542,486
Technology Center 1600

Before ERIC B. GRIMES, DEBORAH KATZ, and,
MICHAEL A. VALEK, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134(a) involving claims to a pharmaceutical composition, which have been rejected as obvious and as containing an improper Markush group. We have jurisdiction under 35 U.S.C. § 6(b).

We AFFIRM.

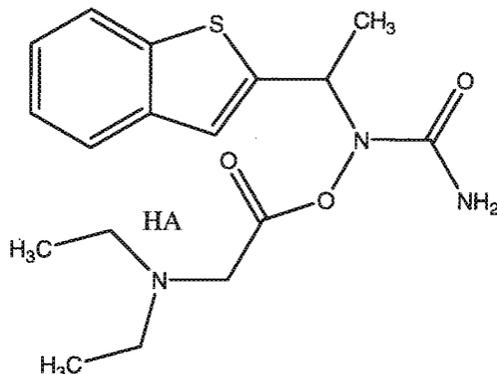
¹ Appellant identifies the real party in interest as TECHFIELDS PHARMA CO., LTD. Appeal Br. 3. We use the word Appellant to refer to “applicant” as defined in 37 C.F.R. § 1.42(a).

STATEMENT OF THE CASE

The “invention relates to the field of pharmaceutical compositions capable of penetrating one or more biological barriers.” Spec. ¶ 2. “One aspect of the invention is directed to a high penetration prodrug (HPP) or a high penetration composition (HPC).” *Id.* ¶ 5. “HPP” or “HPC” refer to “a composition comprising a functional unit covalently linked to a transportational unit through a linker.” *Id.*

“In certain embodiments, a parent drug of an HPP or HPC is a drug that can be used by itself or in combination with other drug(s) to treat pulmonary conditions.” *Id.* ¶¶ 9, 10. Exemplary parent drugs include “5-lipoxygenase inhibitors includ[ing] . . . zileuton [(RS)-N-[1-(1-benzothien-2-yl)ethyl]-N-hydroxyurea].” *Id.* ¶ 12.

Claims 19, 51, 54, 57, and 60 are on appeal. Claim 19 is the only independent claim and is directed to “[a] pharmaceutical composition comprising a pharmaceutically acceptable carrier and one or more compounds selected from a compound of Structure LRA-1 and a compound of Structure 5-LI-1,” where Structure LRA-1 and Structure 5-LI-1 are defined by chemical formulas with variable positions that are selected from certain substituents. Appeal Br. 26–30 (Claims Appendix). In response to an election of species requirement, Appellant elected the species of (RS)-N-[1-(1-benzothien-2-yl)ethyl]-N-(2-diethylaminoacetyloxy)urea hydrochloride, with the following structure:



wherein HA is HCl. Response to Election/Restriction filed March 18, 2016, page 2. The elected species is within the genus defined by Structure 5-LI-1 recited in claim 19.

The claims stand rejected as follows:

Claim 19 on the ground of containing an improper Markush group (Ans. 3) and

Claims 19, 51, 54, 57, and 60 under 35 U.S.C. § 103(a) as obvious based on Trivedi,² Järvinen,³ Mahfouz,⁴ and Walson⁵ (Ans. 7).

² Jay S. Trivedi, *Solubility and stability characterization of zileuton in a ternary solvent system*, European Journal of Pharmaceutical Sciences 4:109–116 (1996).

³ Tomi Järvinen, *Design and Pharmaceutical Applications of Prodrugs*, in *Pharmaceutical Sciences Encyclopedia: Drug Discovery, Development, and Manufacturing*, Shayne C. Gad (ed.), John Wiley & Sons, pp. 1–64 (2010).

⁴ Nadia M. Mahfouz, *Synthesis, chemical and enzymatic hydrolysis, and bioavailability evaluation in rabbits of metronidazole amino acid ester prodrugs with enhanced water solubility*, Journal of Pharmacy and Pharmacology 53:841–848 (2001).

⁵ Philip D. Walson, *Antipyretic Efficacy and Tolerability of a Single Intravenous Dose of the Acetaminophen Prodrug Propacetamol in Children: A Randomized, Double-Blind, Placebo-Controlled Trial*, Clinical Therapeutics 28:762–796 (2006).

OPINION

Improper Markush Group

Claim 19 stands rejected on the ground of containing an improper Markush group, because the Examiner finds that the compounds of Structure 5-LI-1 do not share a single structure similarity with the compounds of Structure LRA-1. Ans. 3–5. Specifically, the Examiner finds:

Compounds of Structure LRA-1 are quinoline class compounds that would be classified under class 546, subclass 112.

Compounds of Structure 5-LI-1 are benzothiophene class compounds that would be classified under class 532, subclass 49. These compounds lack unity of invention since they: do not share a common utility and/or they do not share a substantial structural feature essential to that utility.

Id. at 5–6.

We agree with the Examiner that the compounds of Structure LRA-1 and the compounds of Structure 5-LI-1 do not form a proper Markush group. “A Markush claim contains an ‘improper Markush grouping’ if: (1) The species of the Markush group do not share a ‘single structural similarity,’ or (2) the species do not share a common use.” 76 Fed. Reg. 7162, 7166 (2011) (footnote omitted). “Members of a Markush group share a ‘single structural similarity’ when they belong to the same recognized physical or chemical class or to the same art-recognized class.” *Id.*

Here, the Examiner has found that compounds of Structure LRA-1 are in the quinoline class, while compounds of Structure 5-LI-1 are in the benzothiophene class, and that compounds according to the two structures would be classified differently by the USPTO. The Structure LRA-1 compounds and the Structure 5-LI-1 compounds therefore are not in the same recognized physical or chemical class or the same art-recognized class,

and do not share a “single structural similarity.” *Cf. In re Harnisch*, 631 F.2d 716, 722 (CCPA 1980) (“Clearly, [the claimed compounds] are all coumarin compounds which the board admitted to be ‘a single structural similarity.’”). We thus agree with the Examiner that the inclusion of both compounds of Structure LRA-1 and compounds of Structure 5-LI-1 in the Markush group of claim 19 is improper.

Appellant argues that the Specification describes high penetration prodrugs as comprising a “functional unit” (i.e., a moiety of a parent drug) linked to a “transportational unit.” Appeal Br. 9. Appellant argues that “[t]he specification further explains that ‘[a] transportational unit of an HPP comprises a protonatable amine group that is capable of facilitating the transportation or crossing of the HPP through one or more biological barriers.’” *Id.* at 10. Appellant argues that “each species recited in claim 19 comprises a transportational group (i.e., a protonatable amine group)” because both Structure LRA-1 and Structure 5-LI-1 comprise either Structure W-1 or W-2 and “each of Structure W-1 and Structure W-2 comprises a protonatable amine group. . . . [E]ach Structure comprises a basic nitrogen atom, and each Structure comprises a group ‘HA’ that, in some embodiments, is an acid. Accordingly, each species recited in claim 19 possesses at least these structural similarities.” *Id.* at 10–11.

This argument is unpersuasive. As set out in the Federal Register notice cited by the Examiner, “[m]embers of a Markush group share a ‘single structural similarity’ when they belong to the same recognized physical or chemical class or to the same art-recognized class.” 76 Fed. Reg. at 7166. Appellant has not disputed the Examiner’s finding that compounds

of Structure LRA-1 are quinoline class compounds, while compounds of Structure 5-LI-1 are benzothiophene class compounds. Nor has Appellant pointed to evidence showing that compounds that comprise “a protonatable amine group” or “a basic nitrogen atom” belong to the same recognized physical or chemical class or to the same art-recognized class.

Appellant also argues that the rejection is inconsistent with *In re Harnisch*, because, “[l]ike the claims in *Harnisch*, claim 19 recites compounds belonging to a genus that is defined by the Appellant: namely, one comprising species that each comprise a protonatable amine group.” Appeal Br. 13.

This argument is also unpersuasive. The *Harnisch* court did not hold that the Markush group at issue in that case “belong[ed] to a genus that is defined by the Appellant,” as Appellant argues. Rather, the court concluded that “all of appellant’s claimed compounds are dyes” and “they are all coumarin compounds which the board admitted to be a ‘single structural similarity.’” *Harnisch*, 631 F.2d at 722. Based on these factors, the court stated:

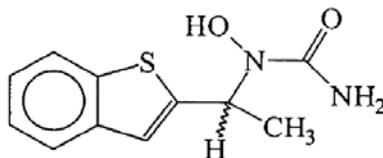
We hold, therefore, that the claimed compounds all belong to a subgenus, as defined by appellant, which is not repugnant to scientific classification. Under these circumstances we consider the claimed compounds to be part of a single invention so that there is unity of invention. . . . The Markush groupings of claims 1 and 3–8 are therefore proper.

Id. That is, because the compounds of the Markush group defined by the appellants in *Harnisch* shared a common use and a single structural similarity, the Markush grouping was proper.

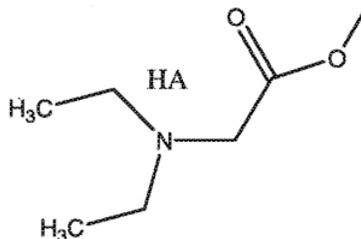
The *Harnisch* court did not hold that a proper Markush group can comprise any genus that an applicant chooses to define. In fact, with regard to Appellant's argument that the compounds of claim 19 all comprise a protonatable amine group, the *Harnisch* court expressly stated that "in determining the propriety of a Markush grouping the compounds must be considered as wholes and not broken down into elements or other components." *Harnisch*, 631 F.2d at 722 (discussing *In re Jones*, 162 F.2d 479 (CCPA 1947)).

Obviousness

Claims 19, 51, 54, 57, and 60 stand rejected as obvious based on Trivedi, Järvinen, Mahfouz, and Walson. The Examiner finds that "Trivedi teaches a composition comprising zileuton [and] water:ethanol (75:25)." Ans. 7. Trivedi discloses the following structure for zileuton:



Trivedi 109, Fig. 1. The Examiner finds that "Trivedi does not teach the . . . zileuton prodrug" of the elected species. Ans. 8. That is, the HO- group of zileuton corresponds to the following structure in the elected species:



See Ans. 8, 27. In other words, the elected species is the N,N-diethyl glycine ester of zileuton. See Ans. 10 ("[I]t would have been *prima facie* obvious . . .

to modify zileuton moiety to comprise a N,N-diethylglycinyl promoiety at the hydroxyl position.”).

The Examiner finds that “Jarvinen teaches prodrugs are commonly derived from existing hydroxyl groups on the parent drug molecule, usually by ester formation” and “N,N-diethyl glycinyl is an example of promoieties for hydroxyl groups.” Ans. 8. The Examiner finds that Järvinen also teaches that “amino acid derivatives such as N-propyl-, N,N-dimethyl, and diethyl glycine esters, . . . were freely water-soluble and their half-lives for bioconversion were less than 30 min[utes].” *Id.* at 9.

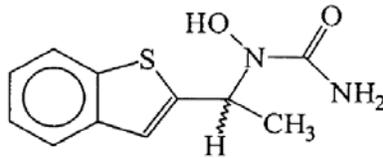
The Examiner finds that “Mahfouz teaches a series of amino acid esters were synthesized as potential prodrugs of metronidazole” and teaches that the “N,N-diethylglycinate hydrochloride derivative[] displayed higher aqueous solubility, which exceeded that of the parent drug by a factor of approximately 140.” *Id.* The Examiner finds that “Walson teaches propacetamol is an acetaminophen prodrug . . . [and] is hydrolyzed to release acetaminophen and pharmacologically inactive N,N-diethylglycine.” *Id.*

The Examiner concludes that it would have been obvious to modify zileuton moiety to comprise a N,N-diethylglycinyl promoiety at the hydroxyl position with an expectation of success, since the prior art establishes that N,N-diethylglycinyl is a promoiety for producing prodrugs commonly derived from existing hydroxyl groups, is known to improve solubility of a parent compound, and to hydrolyze to a parent compound and an inactive N,N-diethylglycine.

Id. at 10.

We agree with the Examiner that the claimed composition, comprising the elected species, would have been obvious to a person of ordinary skill in

the art based on the cited references. Trivedi discloses that zileuton is a drug used to treat asthma, and has the following structure:



Trivedi 109, right col. Trivedi also discloses that “[z]ileuton is [] poorly soluble in water . . . , and the use of pharmaceutically acceptable organic co-solvents might be necessary in liquid formulations that require concentrations of drug above its aqueous solubility limit.” *Id.* at 110, left col. Trivedi “examined the solubility and stability of zileuton in a ternary solvent system consisting of water, ethanol (EtOH), and propylene glycol . . . with the goal of arriving at a solvent composition which optimizes both solubility and chemical stability.” *Id.*

Järvinen states that “[t]he prodrug approach is a valuable tool to further optimize potent structures and to solve potential formulation or delivery problems.” Järvinen 2. Järvinen teaches that “[p]rodrugs are commonly derived from existing hydroxyl groups on the parent drug molecule, usually by ester formation (Fig. 10).” *Id.* at 15.

Järvinen’s Figure 10 shows five “[e]xamples of promoieties for hydroxyl groups,” including *N,N*-Diethyl glyciny. Järvinen, Figure 10 and figure legend. The Examiner finds, and Appellant does not dispute, that modifying zileuton’s hydroxyl group (HO-) by forming the *N,N*-Diethyl glyciny ester results in the elected species of claim 19. *See* Ans. 10, Appeal Br. 19 (disputing that it would have been obvious to make the ester modification but not the identity of the resulting compound).

Järvinen states that “[w]ater-soluble prodrugs are commonly obtained as phosphates, succinates, or *amino acid esters* of the hydroxyl group.” Järvinen 16 (emphasis added). “Amino acid esters, which are substrates for endopeptidases in vivo, are also considered as suitable promoieties that improve aqueous solubility.” *Id.* (endnote omitted). Järvinen states that “[a]mino acid derivatives such as . . . diethyl [sic] glycine esters, . . . were freely water-soluble and their half-lives for bioconversion were less than 30 min.” *Id.* at 17. Järvinen therefore would have provided a skilled artisan with a reasonable expectation that forming the diethyl glycine ester of a hydroxyl group of a parent compound would result in a prodrug with increased water-solubility.

Järvinen states that the chemical stability of amino acid derivatives “was limited. In general, α -amino acid esters tend to be unstable in aqueous solution due to an electron-withdrawing effect of the protonated amino group.” *Id.* Järvinen states that, similarly, “succinate esters have a limited chemical stability, due to intramolecular hydrolytic catalysis of the ester bonds by the neighboring carboxyl group.” *Id.* at 16 (endnote omitted). “These compounds are, therefore, marketed as a freeze-dried powder, which is dissolved just prior to administration.” *Id.*

Mahfouz discloses synthesis and evaluation of “[a] series of amino acid esters . . . as potential prodrugs of metronidazole with the aim of improving aqueous solubility and therapeutic efficacy.” Mahfouz 841, abstract. The “N,N-diethylglycinate hydrochloride . . . displayed higher aqueous solubility, which exceeded that of the parent drug by [a] factor[] of approximately 140.” *Id.* Mahfouz states that “[t]he prodrugs exhibited

adequate chemical stability (half-life, $t_{1/2}$, 4–15 h) in aqueous phosphate solution of pH 7.4.” *Id.* “In conclusion, the designed amino acid esters . . . might be considered as good candidates for water-soluble prodrug forms of metronidazole.” *Id.*

Walson states that, “[u]ntil recently, . . . the only IV formulation of acetaminophen was the acetaminophen prodrug propacetamol hydrochloride.” Walson 763, left col. “This product must be dissolved in saline or glucose just before infusion. Propacetamol is rapidly and completely hydrolyzed in the blood into acetaminophen and pharmacologically inactive *N,N*-diethylglycine by plasma esterases.” *Id.*

Based on these teachings, it would have been obvious to a person of ordinary skill in the art to modify zileuton by forming the *N,N*-diethyl glycine ester at the hydroxyl group, resulting in the elected species of compound. The references provide adequate reason to combine their teachings, because Trivedi teaches that zileuton is useful for treating asthma but has poor aqueous solubility, and Järvinen teaches that water-soluble prodrugs are commonly obtained as amino acid, including diethyl glycine, esters of a parent drug. Järvinen also teaches that diethyl glycine derivatives were found to be “freely water-soluble.” Järvinen 17. Mahfouz similarly teaches that the diethyl glycine ester of metronidazole increased solubility by a factor of 140. Mahfouz 841, abstract. The cited references thus would have provided a reasonable expectation that the diethyl glycine ester of zileuton would have increased water-solubility compared to the parent compound.

Appellant argues, however, that “Jarvinen cautions its reader against risks of *decreased* chemical stability resulting from prodrug formation, including the structural modification proposed by the Office.” Appeal Br.

19. That is,

[t]he person having ordinary skill in the art would understand that N,N-diethyl glycine ester is an example of an α -amino acid ester. Thus, Jarvinen plainly identifies the diethyl glycinyl ester moiety as one that suffers from reduced chemical stability. Further still, Jarvinen also highlights the instability of α -amino acid esters (such as N,N-diethyl glycine ester) in *aqueous solution*.

Id.

Consistent with Appellant’s argument, Järvinen states that the chemical stability of amino acid derivatives “was limited” and that α -amino acid esters generally “tend to be unstable in aqueous solution.” Järvinen 17. However, Järvinen notes that succinate esters also tend to have limited stability, which simply requires that they be marketed as a freeze-dried powder that is dissolved just prior to administration. *Id.* at 16.

Thus, a skilled artisan would have viewed the limited chemical stability disclosed by Järvinen as likely to require formulating the elected species of compound as a dry powder, but would not have expected the limited stability to make the compound unusable therapeutically. Walson, in fact, discloses that propacetamol is an acetaminophen prodrug used clinically and formulated in just this way.

We therefore do not agree with Appellant that Järvinen’s discussion of the chemical stability, in aqueous media, of amino acid ester prodrugs would have dissuaded a skilled artisan from making the combination proposed by the Examiner.

Appellant also argues that there would not have been a reason to combine the teachings of Trivedi and Järvinen because Järvinen pertains almost exclusively to prodrug design and synthesis, while Trivedi is “concerned with the formulation of an active agent (*e.g.*, in a specific solvent composition).” Appeal Br. 16–17. “Trivedi and Jarvinen contemplate entirely different approaches to overcoming poor drug properties and explore them in different contexts. . . . The references thus direct their readers to different methods of improving drug properties, and neither reference teaches or suggests the approach adopted by the other.” *Id.* at 17.

This argument is also unpersuasive. Järvinen states that “[t]here are various approaches that can be applied to overcome poor properties of drug formulation and delivery. Some of these problems can be overcome by dosage form design. . . . An important strategy approach to improve poor drug formulation and delivery properties is prodrug technology.” Järvinen 2. Thus, Järvinen provides evidence that Trivedi’s approach of changing the solvent composition, and Järvinen’s approach of making prodrug forms of an active agent were both known methods of addressing poor properties of a drug, such as low solubility in aqueous media. A skilled artisan therefore would have recognized Järvinen’s prodrug approach as being among the obvious methods of addressing the poor water-solubility of zileuton.

DECISION SUMMARY

In summary:

Claims Rejected	35 U.S.C. §	Reference(s)/Basis	Affirmed	Reversed
19		Improper Markush Group	19	
19, 51, 54, 57, 60	103(a)	Trivedi, Järvinen, Mahfouz, Walson	19, 51, 54, 57, 60	
Overall Outcome			19, 51, 54, 57, 60	

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). *See* 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED