2018 Pat. App. LEXIS 3698

Patent Trial and Appeal Board

May 15, 2018, Decided

Appeal 2016-006661; Application 13/312,371 [1] ; Technology Center 1600

Reporter
2018 Pat. App. LEXIS 3698 *

Ex parte ROBERT EUGENE and BING LI

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

enantiomers, compound, technology, column, chiral, racemate, diacylhydrazines, teach, biological, screen, prior art, routine, ordinary skill, chromatography, phase, invent, double-patenting, unpredictable, predictable, accomplish, discovery, formula, enantioselective, ***pharmaceutical***, sequence, rejected claim, trial-and-error, conventional, pesticide, eluent

Panel: Before RICHARD M. LEBOVITZ, RYAN H. FLAX, and DAVID COTTA, Administrative Patent Judges.

Opinion By: RICHARD M. LEBOVITZ

Opinion

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal involves claims directed to enantiomerically enriched compounds of the general Formula III. The Examiner rejected the claims as obvious under 35 U.S.C. § 103 and on the ground of non-statutory double-patenting. Appellants appeal the rejections pursuant to 35 U.S.C. § 134. We have jurisdiction under 35 U.S.C. § 6(b). The rejections are affirmed.

STATEMENT OF THE CASE

An oral hearing was held on April 3, 2018. The transcript of the hearing will be entered into the record in due course.

Claims 3, 17, 20, and 27 are appealed. Appeal Br. 4.

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[1] The Appeal Brief ("Appeal Br.") 4 lists Intrexon Corporation, as the real party-in-interest.

The claims stand rejected by the Examiner, as indicated in the Examiner's Answer ("Ans."), as follows:

1. Claims 3, 20, and 57 on the ground of nonstatutory obviousness-type double-patenting as obvious over claims 1-4 of Hormann '161 **[*2]** (U.S. Pat. No. 7,304,161 B2, issued Dec. 4, 2007) in view of Hsu (U.S. Pat. No. 6,013,836, issued Jan. 11, 2000), Zhang (*Drug Discovery Today*, 10(8):571-577, April 2005), and Chiral Technologies (*Laboratory Products and Services for Chiral Analysis and Separation*, 2006 Edition). [2] Ans. 3.

2. Claims 3, 17, 20, and 57 on the ground of nonstatutory obviousness-type double-patenting as obvious over claims 1 and 2 of Hormann '315 (U.S. Pat. No. 7,456,315 B2, issued Nov. 25, 2008) in view of Hsu, Zhang, and Chiral Technologies. Ans. 4.

3. Claims 3, 20, and 57 on the ground of nonstatutory obviousness-type double-patenting as obvious over claims 1 and 3-7 of Hormann '962 **[*3]** (U.S. Pat. No. 5,482,962, issued Jan 9, 1996) in view of Hsu, Zhang, and Chiral Technologies. Ans. 5.

4. Claims 3, 20, and 57 provisionally on the ground of nonstatutory obviousness-type double-patenting as obvious over claims 1, 2, and 15 of co-pending Application No. 13/603,965 in view of Hsu, Zhang, and Chiral Technologies. Ans. 7.

5. Claims 3, 17, 20, and 57 on the ground of nonstatutory obviousness-type double-patenting as obvious over claims 1 and 2 of Hormann '948 (U.S. Pat. No. 8,524,948 B2, issued Sep. 3, 2013) in view of Hsu, Zhang, and Chiral Technologies. Ans. 8.

6. Claims 3, 17, 20, and 57 under pre-AIA 35 U.S.C. § 103(a) as obvious over Hormann '146 (U.S. Pat. Appl. Publ. 2006/0020146 A1, Jan. 26, 2006) in view of Hsu, Zhang, and Chiral Technologies. Ans. 10.

7. Claims 3, 17, 20, and 57 under pre-AIA 35 U.S.C. § 103(a) as obvious over Berger (*J. Am. Chem. Soc.*, 2003, 125: 9596-9597) in view of Hormann '146, Feringa (*Stereoselectivity of Pesticides: Biological and Chemical Problems*, 1988, Chapter 15, p. 453-499), Hsu, and Leighton **[*4]** (WO 03/074534 A1, publ. Sep. 12, 2003). Ans. 11.

CLAIMS

Claim 3, which is the only independent claim on appeal, is directed to an enantiomerically enriched compound of Formula III. The formula represents a genus of compounds and is reproduced in the Claim Appendix. Claim 17, which depends from claim 3, recites specifically named compounds which are species of the genus of compounds of claim 3.

DOUBLE-PATENTING REJECTIONS

There are five obvious-type double-patenting rejections listed in the Examiner's Answer. *See* Rejections 1-5 listed above. Appellants did not provide different arguments for any of the five pending double-patenting rejections together. Consequently, we have addressed them together.

Rejections

The Examiner found that each of the cited patents and patent applications are directed to the same compounds which are claimed, but differ in not requiring an "enantiomeric enriched compound" where "the compound has an enantiomeric excess of at least 95%" as recited in independent claim 3. To meet this limitation, the Examiner cited Hsu, Zhang, and Chiral Technologies as evidence of a reason to separate enantiomers, the technology to do so, and of a reasonable expectation **[*5]** of success. Final Action ("Final Act.") 3-4.

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[2] There are two excerpts from Chiral Technologies: one excerpt had numbered pages, but the second excerpt did not. The second excerpt contained a list of LC columns available from Chiral Technologies.

Findings of Fact ("FF")

FF1.

Molecular chirality is a fundamental consideration in drug discovery, one necessary to understand and describe biological targets as well as to design effective ***pharmaceutical*** agents. Enantioselective chromatography has played an increasing role not only as an analytical tool for chiral analyses, but also as a preparative technique to obtain pure enantiomers from racemates quickly from a wide diversity of chemical structures. Different enantioselective chromatography techniques are reviewed here, with particular emphasis on the most widespread high performance liquid chromatography (HPLC) and the rapidly emerging supercritical fluid chromatography (SFC) techniques. This review focuses on the dramatic advances in the chiral stationary phases (CSPs) that have made HPLC and SFC indispensable techniques for drug discovery today.

Zhang 571 (abstract)

FF2.

It is not uncommon for one enantiomer to be active while the other is toxic in biological systems. Thus, the FDA has required evaluation of each enantiomer in developing stereoisomeric drugs. As a. result, the ***pharmaceutical*** industry has raised its **[*6]** emphasis on the generation of enantiomerically pure compounds before undertaking pharmacokinetic, metabolic, physiological and toxicological evaluation in the search for drugs with greater therapeutic benefits and low toxicity. According to the recently survey by Israel Agranat, the distribution of worldwide approved drugs from 1983-2002 and FDA-approved drugs from 1991 2002 indicate that single-enantiomers surpassed achirals whereas racemic drugs represented the minority category.

Zhang 571.

FF3.

Although a large number of approaches have been used to isolate single enantiomers, enantioselective chromatography using HPLC and SFC on chiral stationary phases (CSPs) has become the most widely utilized technique in the context of obtaining limited quantities (from mg to multi-grams) of pure enantiomers quickly, particularly in drug discovery. The impetus for reliance on chromatography has been fueled by recent advances in CSPs that allow reliable, robust and efficient resolution of mg to gram quantities of chiral molecules in a matter of hours.

Zhang 571.

FF4.

It is estimated that 1300 CSPs have been prepared, and over 200 CSPs have been commercialized. Thus, understanding **[*7]** and classifying the different CSPs is important for selecting the most suitable CSP to solve a particular problem

Zhang 573.

Strategies for fast enantioselective method development in drug discovery

Enantioselective chromatography has advanced dramatically in the past two decades, led by the development of new CSPs. However, the demand for faster preparative and analytical chiral resolutions for a wide variety of new chemical entities continues to push the frontiers of current technologies. As there is no universal CSP, elucidation of the chiral recognition mechanisms operating at the molecular level is essential for further development in the field.

Zhang 575.

FF6.

Currently, prediction of enantioselectivity for almost any CSPs is, practically speaking, still not feasible. In addition, small changes in solute structure and/or chromatographic environment often have great impact on the chiral resolution ability of many CSP. Consequently, 'trial-and-error' screening of a set of CSPs that offers a

broad-spectrum of enantioselectivity in simple mobile phase systems has been the most popular approach to chiral method development in drug discovery.

Zhang 575. **[*8]**

FF7.

To facilitate this approach, three automated column screening strategies have been reported.

Zhang 575.

FF8.

Very recently, a multi-column parallel screening approach with a circular dichroism signal pooling technique was reported. Five CSPs were screened simultaneously in parallel using a simple customized HPLC system with five U V detectors and one circular dichroism detector. An injected sample was carried by the mobile phase through an on-line pre-filter, then divided into five columns and UV detectors with even flow distribution accomplished via individually adjusted backpressures. . . As shown in Figure 2, the enantioselectivity of sulconazole was screened on five CSPs in parallel resulting in a fivefold increase in throughput.

Zhang 575.

FF9.

Figure 2 in Zhang is reproduced below:

Figure 2 shows 5 columns used to separate sulconazole into enantiomers; 3 of the columns achieve good separation (AS-H, OD-H, OJ-H).

FF10.

Enantioselective chromatography, particularly HPLC and SFC on CSPs, has become an indispensable part of drug discovery not only for chiral analyses **[*9]** but also for the fast preparation of drug molecules.

Zhang 576.

FF11.

Since the founding of Chiral Technologies Inc., applications for chiral chromatography have grown significantly. We have seen a dramatic increase in demand for chiral columns . . . and outsourcing services to rapidly obtain pure enantiomers through chromatography. ***Pharmaceutical*** industry customers . . . have come to reply on chromatographic resolution technology for the fastest separation of racemic compounds as a visible and economical route to commercial development.

Chiral Technologies 2.

FF12.

In addition, our Methods Development laboratory gives us the ability to screen clients' compounds under confidentiality for analytical applications or for potential large-scale applications with a library of over 50 proprietary CSP.

Chiral Technologies 2.

FF13.

The key to effective chiral separation is the CSP. Chiral Technologies offers the products and services to assist customers in selecting the optimum columns and phases for their chiral separation.

Through our fee based Application Service, we assist customers in identifying the column that offers optimal resolution for analysis.

[*10]

Chiral Technologies 7.

FF14.

> The Separation Services Group at Chiral Technologies offers rapid isolation of pure enantiomers from racemic mixtures . . . . Our expertise in both HPLC and FC techniques allows us to develop the fastest and most economical process for a separation project.

Chiral Technologies 7.

> FF15.
>
> Figure 7 shows the increased success rate due to the introduction of the newer CHIRALPAK ID phase into a column screen of 123 compounds using a single eluent combination of hexane -- 2-PrOH. When these immobilized phase columns are used with the set of four primary screening solvents, the separation success rate can approach 99%. If the desired chiral separation is not achieved, then an extended secondary screen can be applied.

Chiral Technologies (unnumbered page but in section titled "LC columns --Chiral Technologies")

> FF16.
>
> It will be appreciated by those skilled in the art that electronic forces may give rise to more than one isomer of the compounds of Formula II such as enantiomers, conformers and the like. There may be a difference in properties such as physical characteristics and degree of biological activity between such isomers. Separation **[*11]** of a specific isomer can be accomplished by standard techniques well known to those skilled in the art such as silica gel chromatography.

Hsu 21:18 25.

> FF17.
>
> Enantioselective biological recognition or biodiscrimination of chiral pesticide enantiomers is often observed in biological systems. . . Despite of the fact that the individual enantiomers of chiral pesticides may show different bioactivity, toxicity, and environmental behaviors, most of the chiral compounds are sold and used in the form of racemates. There will be legislative requirements for the analysis of individual enantiomers during registration of techniques in the future.

Wang [3] 602.

Discussion

Appellants contend that it was unpredictable that chiral HPLC (high pressure liquid chromatography) separation would successfully separate the racemates (a mixture of left- and right-handed enantiomeric) diacylhydrazines described in the cited Hormann patents and **[*12]** publications into the claimed enantiomeric enriched compounds of claim 3 (Appeal Br. 14). Appellants argue that, "simply because "racemic diacylhydrazines" are disclosed, "does not guarantee the general chiral HPLC techniques of Zhang *et al.* and Chiral Technology can be applied to separate diacylhydrazine enantiomers in the absence of undue experimentation" (*id.*; FF16).

The Examiner's principal evidence that it would have been predictable that the racemates cited in Rejections 1-5 could be separated into enantiomers is based on the teachings in Zheng and Chiral Technologies that have been summarized in Findings of Fact 1-15. Briefly, both publications describe the widely used technologies utilized at the time of the invention to separate enantiomers that are present in a racemate. In the Appeal Brief, Appellants point to specific examples in which poor separation was achieved utilizing a specific CSP column (Appeal Br. 14), but Appellants did not address the broader teachings in each of the publications that it was conventional to try different CSP columns and solvents simultaneously to identify an effective one (or several) as expressly taught in the cited prior art (FF6, **[*13]** FF7, FF8, FF12, FF13, and FF14).

Zhang specifically teaches a trial-and-error approach to identifying an effective column for separating enantiomers from a racemate, namely where different columns are tried until a column is found that successfully separates the enantiomers (FF6). Appellants contend that the "trial-and-error approach" described in Zhang was

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[3] Wang et al., *J. Chromatographic Science*, 44: 602-606. November--December 2006.

not "legally sufficient to prove obviousness. " Appeal Br. 15. Appellants rely on KSR International Co. v. Teleflex Inc. 550 US 398, 421 (2007), and the line of cases that follow it, to support this argument. Appellants state:

> Zhang *et al.* and Chiral Technology teach general chiral HPLC techniques, but provide no direction as to which of the many possible chiral HPLC choices, e.g., CSP type, eluent, and flow rate, are likely to successfully resolve chiral diacylhydrazines. According to Zhang *et al.*, over 200 CSPs are commercially available. *See* Zhang *et al.*, p. 573.

Appeal Br. 16.

Appellants contend that Zhang provides no direction to "as to which of the many possible chiral HPLC choices . . . are likely to successfully resolve chiral diacylhydrazines, " but Appellants do not **[*14]** explain how this establishes unpredictability or lack of a reasonable expectation of success. Zhang recognizes that there is no universal CSP (FF5), and teaches that there are a "large number of approaches that have been used," including "1300 CSPs and over 200 CSPs [which] have been commercialized" (FF4). However, Zhang teaches that it is conventional, and the "most popular approach," to try different CSP columns to determine an effective one to accomplish separation ("trial-and-error" screening) (FF6). Zhang identifies several automated approaches to identify a CSP column to separate out enantiomers (FF6--FF8). Zhang gives one example in which five CSP columns were used in a trial and error experiment to find a column that worked, and indeed success was achieved with three columns (FF9). Thus, while an individual CSP column may fail, Zhang teaches using multiple "broad-spectrum" CSPs (FF6) to identify an effective one to accomplish enantiomer separation.

Appellants also assert that the Chiral Technologies product catalog also establishes unpredictability, arguing:

> Chiral Technology disclose the separation of 18 different solutes using 18 different eluents and 6 different flow **[*15]** rates. *See* the chromatograms of Figures 1-5, 9-13, and 15-22 of Chiral Technology. Multiplying 200 chiral columns by 18 different eluents and 6 different flow rates gives the possibility of 21,600 trial-and-error experiments suggested by the prior art needed to resolve any given solute. This number is well beyond the *KSR* prong requiring the field of search to be among a "finite number of identified" solutions. KSR, 550 U.S. at 421.

Appeal Br. 16.

This argument is not persuasive. The figures identified by Appellants in Chiral Technologies appear to be individual experiments performed using a single column, eluent, and flow-through rate on a compound of interest. For example, Figure 1, reproduced below, represents chiral separation of a single compound of interest:

Figure 1 shows the enantiomer separation of a compound. [4]

[*16]

Appellants have not explained why individual experiments to show the success of each of the columns in Chiral Technologies constitutes a teaching 21,600 experiments. There is no direction in Chiral Technologies that each of the disclosed different eluents and flow rates are necessary to test on each CSP column. Appellants' calculation that "21,600 trial-and error experiments suggested by the prior art needed to resolve any given solute" is not factually supported because it is derived from an artificial calculation from unrelated experimental data, and, in fact, is inconsistent with Zhang, which teaches the success of a five CSP column approach to separate a compound of interest (FF8, FF9).

As discussed by Appellants, a factor to be considered in making an obviousness determination is whether there were "a finite number of identified, predictable solutions" available to one of ordinary skill in the art that would have

[4] The quality of the figure represents the quality of the copy of Chiral Technologies provided to the USPTO by Appellants and entered by the USPTO into the record.

routinely led to the claimed invention. This factor is couched in the context of whether it was "obvious to try" to make the claimed invention. As held by the U.S. Supreme Court in KSR, 550 U.S. at 421:

> When there is a design need or **[*17]** market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Expanding on this analysis, the Federal Circuit, in Unigene Labs., Inc. v. Apotex 655 F.3d 1352, 1361 (Fed. Cir. 2011), explained:

> To render a claim obvious, prior art cannot be "vague" and must collectively, although not explicitly, guide an artisan of ordinary skill towards a particular solution. Bayer Schering, 575 F.3d at 1347. Indeed, "most inventions that are obvious were also obvious to try," *id.*, and a combination is only obvious to try if a person of ordinary skill has "a good reason to pursue the known options." KSR, 550 U.S. at 421 []. When a field is "unreduced by direction of the prior art," and when prior art gives "no indication of **[*18]** which parameters were critical or no direction as to which of many possible choices is likely to be successful," an invention is not obvious to try. Bayer Schering, 575 F.3d at 1347 (citing In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988)); *see also* Ortho-McNeil, 520 F.3d at 1364 (stating the number of options must be "small or easily traversed").

Thus, we consider whether the claimed invention would have been arrived at by following a routine and predictable path described in the prior art.

As discussed by Zhang, there have been "dramatic advances in the chiral stationary phases (CSPs) that have made HPLC and SFC indispensable techniques for drug discovery" (FF1). Zhang discloses that the "FDA has required evaluation of each enantiomer in developing stereoisomeric drugs," resulting in the ***pharmaceutical*** industry's "emphasis on the generation of *enantiomerically pure compounds* before undertaking pharmacokinetic, metabolic, physiological and toxicological evaluation" (FF2) (emphasis added' Zhang also describes a survey showing "that single-enantiomers surpassed achirals whereas racemic **[*19]** drugs represented the minority category" (FF2). Thus, it cannot be said that the discovery or desirability of pharmacologically active enantiomers was rare nor a new, unexplored area, Rather, the FDA's requirements and the number of existing enantiomer pure drugs at the time of the invention indicates that the technology to make enantiomerically pure compositions was well known to the ordinary skilled artisan. This conclusion is buttressed by the extensive disclosures in Zhang and Chiral Technologies describing the "large number of approaches [which] have been used to isolate single enantiomers" (FF3).

Moreover, Zhang is a review article describing the "widely utilized techniques" for obtaining enantiomer pure compounds (FF3), not a report on some new technique. Zhang discloses that 1300 CSPs (columns to separate enantiomers) have been prepared and that over 200 are commercially available (FF4). Further, Chiral Technologies is a product and services catalog describing a large number of different commercially available CSP columns and commercial separation services (FF12--FF14). Thus, at the time of the invention, technology was widely available to achieve enantiomer separation.

Zhang **[*20]** acknowledges that which CSP column will work to achieve enantiomeric separation on a given racemate compound cannot be predicted *theoretically* (F176). However, Zhang does not indicate there was any doubt that the existing technology would *practically* achieve success and described various automated screening to facilitate the process of trying different CSPs to identify the one that worked (FF7, FF8). While Appellants point to individual failures of a specific CSP column (Appeal Br. 14), Appellants did *not* identify a racemate that could not be separated into enantiomers by the existing techniques, and as disclosed by Zhang, "a multi-column parallel screening approach" showed success in 3 of the 5 CSP's used for the same compound (FF9).

Consistent with Zhang, Chiral Technologies describes the "dramatic" demand for chiral columns to separate enantiomers and the ***pharmaceutical*** industry's reliance on it (FF11). Chiral Technologies describes their service to customers for "rapid isolation of pure enantiomers from racemic mixtures" (FF14). Figure 7 of Chiral

Technologies shows that a limited selection of columns and screening solvents can achieve a. high success rate of chiral **[*21]** separation (FF15), directly' rebutting Appellants' statements that Chiral Technologies needed 21,600 trial and error experiments to accomplish the same (Appeal Br. 16).

Appellants argue that it was unpredictable that the claimed enriched enantiomers could have been separated (Appeal Br. 14). To support this argument, a declaration was provided under 37 C.F.R. § 1.132 by Robert E. Hormann, Ph.D., a co-inventor of the '371 Application ("Hormann Decl.") Appellants contend that the declaration establishes that separation of the diacylhydrazines was unpredictable at the time of the invention (Appeal Br. 17). Appellants state that one specifically named compound within the scope of the claim "has extremely poor separation characteristics and loading capacities on various Chiralcel columns" (*id.* at 18). Appellants further state that this result, showing "the difficulty found in resolving (+/-)-3,5-dimethyl-benzoic acid N-(1-tert-butyl-butyl)-N'-(2-ethyl-3-methoxy-benzoyl)-hydrazide, applies to the entire genus of compounds having Formula III. The Office has provided no evidence to the contrary" (*id.*).

Dr. Hormann states that he contacted PDR-Chiral **[*22]** Report Inc. ("Report") to separate the above-identified racemate compound into the R and S enantiomers (Hormann Decl. PP 2, 3). Dr. Hormann states that seven columns with a variety of mobile phases were used to separate the compound (*id.* at P 4). Dr. Hormann states that "extensive trial-and-error testing using various columns, mobile phases, and flow rates led PDR-Chiral to conclude" that the compound "'has extremely poor separation characteristics' (*id.* at P 5). Dr. Hormann further states that only one column and set of conditions worked to completely resolve the compound into the enantiomers (*id.*).

We have considered these arguments, but do not find them persuasive. As discussed by Dr. Hormann, the report stated that the compound "has extremely poor separation characteristics" (page 1 of "Report" attached to Hormann Declaration). However, of the seven columns tested, one worked to achieve "Complete resolution" (Report 1). Thus, even a compound characterized as having "extremely poor separation characteristics" could be separated.

The Report further stated that: "Very low loading was utilized, and therefore the method used to separate the enantiomers is not ideally suited **[*23]** for preparative separation" (Report 2). However, the latter statement appears to be relevant only when preparing larger quantities of the enantiomers, and does not disparage the fact the enantiomers were successfully separated utilizing one of the seven columns tested. The fact the seven columns were used, along with different conditions, does not establish unpredictability, but rather reflects the same point as the Zhang and Chiral Technologies teachings, namely, that a set of columns and conditions were routinely tried to identify an effective CSP column to accomplish enantiomeric separation (FF6, FF12, FF13).

It is well-established that absolute predictability is not the hallmark of obviousness. In re Kubin, 561 F.3d 1351, 1360 (Fed. Cir. 2009). In *In re Kubin*, the rejected claim was directed to an isolated nucleic acid coding for an amino acid sequence of the NAIL protein. Id. at 1354. The nucleic and amino acid sequences of the NAIL gene were unknown. The Examiner had rejected the claim as obvious based on a known nucleic acid cloning method. *Id.* The Board affirmed the Examiner, and the applicant appealed to **[*24]** the Federal Circuit. In affirming the Board's decision, the Federal Circuit recognized that the cited prior art publications in the rejection did not disclose the nucleic acid sequence of NAIL. Id. at 561 F.3d at 1361. The court explicitly acknowledged that Kubin disclosed this sequence for the first time. *Id.* However, the court found that the gene had been cloned routinely using available starting materials. Id. at 561 F.3d at 1360. Based on these facts, the court held it would have been obvious to one of ordinary skill in the art to have cloned the NAIL gene with a reasonable expectation of success. Id. at 561 F.3d at 1360-61. Thus, although the claimed NAIL sequence *could not be predicted*, the sequence was determined to be obvious because a known and routine method had been used to clone it and it was predictable that such cloning method would have successfully culminated in ascertaining the claimed sequence.

The principles enunciated in *Kubin* are applicable here because separating enantiomers could be accomplished using the known and routine methodology described in Zhang and **[*25]** Chiral Technologies. Thus, while we have fully considered Appellants' arguments and Dr. Hormann's testimony, it has not been persuasively demonstrated that enantiomeric separation of the identified compound required anything more than routine experimentation using the conventional technology available to one of ordinary skill in the art at the time of the

invention. Indeed, the evidence from two companies offering services in enantiomeric separation, PDR-Chiral and Chiral Technologies, suggest that enantiomeric separation technology was well developed and routine. (FF12--FF14).

The evidence of failure described by Dr. Hormann was for *individual* CSP columns, [5] not for the technology as a whole. To the contrary, the overall strategy of Zhang and Chiral Technologies in using multiple CSP columns to accomplish separation of Dr. Hormann's compound worked (*see also* Final Act. 10). Appellants did not identify any difficulty in the separation technology that required non-routine experimentation outside the conventional techniques described in the prior art. Indeed, Chiral Technologies explicitly disclosed a high success rate using a limited number of columns (FF15), as did Zhang **[*26]** (FF9).

Moreover, even if the one compound described by Dr. Hormann had extremely poor separation characteristics and was difficult to separate into enantiomerically pure compositions, we agree with the Examiner that Appellants have not demonstrated that this result is commensurate with the full scope of the claim, namely, that other compounds in the scope of the claim would have the same alleged difficulty. Appellants contend they would, but provide no evidence or scientific reasoning to support their contention (*see* Appeal Br. 18).

Wang

Appellants contend that the publication by Wang supports the conclusion that chiral HPLC is unpredictable because, of nine pesticides, only three were resolved by Wang (Appeal Br. 14-15). While it is true that only three enantiomers were completely resolved, Wang utilized only one type of column and one mobile phase in order to determine the effect of solvent concentration and **[*27]** temperature on separation. Wang 602 (second column) . However, it is not surprising or unpredictable that a. single column may not be effective for separating all nine enantiomers. Zhang teaches screening a set of CSPs to find one that is effective to separate a racemate, and describes several approaches to testing more than one CSP at once (FF4, FF6-178' Figure 2 of Zhang shows one such approach on sulconazole, where five columns were tested and three achieved enantiomer separation (FF9; Answer 17). Chiral Technologies also describes the same approach of using multiple columns to identify one to achieve effective separation (FF12--FF15).

Chankvetadze [6]

Appellants cited Chankvetadze as evidence of unpredictability, stating the publication "achieve[d] baseline enantioseparation of only four out of eighteen randomly selected chiral drugs and drug analogs on a Chiralcel OJ column using methanol as the mobile phase. " Appeal Br. 15. However, as **[*28]** discussed above, it would not have expected that just one CSP column would be effective in separating all eighteen chiral drugs because, as discussed in both Zhang and Chiral Technologies, the conventional approach is to test more than one CSP to identify an effective one (FF6-11.79, FF12, FF15). Zhang expressly states that there is no universal CSP, requiring a set of CSPs to be screened (FF5, FF6). Thus, Chankvetadze is not inconsistent with the broader and more general teachings in Zhang and Chiral Technologies.

Suminary

Accordingly for the foregoing reasons, the obvious-type double-patenting rejection of claims 3 and 17 is affirmed. Claims 20 and 57 were not argued separately and fall with claims 20 and 57. 37 C.F.R § 41.37(c)(1)(iv).

OBVIOUSNESS REJECTION BASED ON HORMANN '146

The Examiner also rejected claims 3, 17, 20, and 57 as obvious, citing Hormann '146 for the racemate compound and Hsu, Zhang, and Chiral Technologies for the methodology to separate it into enantiomers.

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[5] *See* Appeal Br. 19 (citing evidence of failure as negating a reasonable expectation of success).

[6] Chankvetadze et al., *J. Pharma. Biomed. Anal.*, 27 (2002), 467-478.

Appellants contend that the Examiner made at least two errors. First, Appellants contend that person having ordinary skill in the art would not have selected RG-115830 **[*29]** (the compound cited by the Examiner as within the scope of claim 3) from Hormann '146 as a lead compound (Appeal Br. 20). Second, Appellants contend that the cited publications "do not enable a person having ordinary skill in the art to make diacylhydrazines having an ee of at least 95%" (*id.*). The latter argument is the same argument that was addressed above as not persuasive, and thus we reference our discussion above without additional explanation.

The Examiner cited a compound, RG-115830, in Hormann '146 as within the scope of the claims (Final Act. 11, 12). The Examiner further cited Hsu for its teaching that compounds having this structure can exist as enantiomers that can be routinely separated (Final Act. 11). Zhang and Chiral Technologies were cited as evidence that enantiomeric separation techniques were conventionally utilized in the prior art (*id.*). In the Final Action, the Examiner stated that that there would have been reason to pick this compound because it was more potent than another compound which differed only by a butyl group (*id.* at 12-13). In the Answer, the Examiner stated that the rejection is not based on selecting a lead compound, but rather on **[*30]** separating the racemic diacylhydrazines of Hormann '146 into enantiomers (Ans. 29). The Examiner found that one of ordinary skill in the art would have selected RG-115830 because it is active as shown by the data in Hormann '146 (*id.* at 29-30).

Appellants contend that one of ordinary skill in the art would not have selected RG-115830 as a lead compound because it "is not the most potent compound in *any* of the biological assays used by Hormann ['146] to measure reporter gene expression" (Appeal Br. 22). Appellants further argued that the selection of a lead compound is guided by the evidence of compound's properties, not structural similarity (Reply Br. 8).

Appellants' arguments do not persuade us the Examiner erred.

It is well-established that enantiomers are known to have different properties, and ***pharmaceuticals*** are often based on enantiomers (FF1, FF2), providing a strong reason to have separated a racemate into enantiomers. *See* also FF16, FF17. The issue is whether one of ordinary skill in the art would have selected RG-115830 as a compound to separate into enantiomers.

Appellants' contention that RG-115830 is not the most potent compound in any of the assays tested, **[*31]** and therefore not a candidate for enantiomer separation, is not persuasive.

Hormann '146 describes a genus of compounds as having useful biological activity. (Hormann '146 P 465). RG-115830 appears among a list of compounds shown to have biological activity in several different assays in which they were tested (id. at P 480 (Table 7; p70); P 481 (Table 8, p74); P 489 (Table 9, p.76); P 490 (Table 10 listing ten compounds)). While RG-115830 is biologically active, its activity is not the best of all those compounds surveyed (*id.*; Appeal Br. 22). The reason to *choose* RG-115830 is that it is a biologically-active compound. The reason to *separate* RG-115830 into enantiomers is that "[i]t is not uncommon for one enantiomer to be active while the other is toxic in biological systems. Thus, the FDA has required evaluation of each enantiomer in developing stereoisomeric drugs" (FF2). *See also* FF16, FF17 ("Enantioselective biological recognition or biodiscrimination of chiral pesticide enantiomers is often observed in biological systems. . . individual enantiomers of chiral pesticides may show different bioactivity, toxicity **[*32]** . . . There will be legislative requirements for the analysis of individual enantiomers . . . in the future")

The RG-115830 compound does not require further chemical modification and it is not the starting point to make a structurally different compound as was the compound in the line of "lead compound" cases represented by Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353 (Fed. Cir. 2008) and Otsuka ***Pharmaceutical*** Co., Ltd. v. Sandoz, Inc., 678 F.3d 1280 (Fed. Cir. 2012). Rather, in this case, the compound RG-115830 was made; it needed no modification. The compound included both enantiomers. The only step required was purification, a step the preponderance of the evidence, as discussed in detail above, establishes was routine at the time invention.

For these reasons, we are not persuaded that the alleged inferior activity of RG-115830 would not have made it a candidate for enantiomeric separation. RG-115830 was made by Hormann '146 and all that was required was to separate it into the enantiomeric forms. The lead compound analysis is not applicable in this case. One of ordinary

skill in the art would have routinely **[*33]** separated any of the biologically active enantiomers for the reasons described in Zhang and Chiral Technologies. As held in *In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003), there is a "normal desire of scientists or artisans to improve upon what is already generally known." Such improvement was known to be accomplishable by enantiomeric purification.

Accordingly for the foregoing reasons, the obviousness rejection of claims 3 and 17 is affirmed. Claims 20 and 57 were not argued separately and fall with claims 20 and 57. 37 C.F.R § 41.37(c)(1)(iv).

REJECTION BASED ON BERGER

The Examiner found that it would have been obvious to one of ordinary skill in the art to have synthesized an enantiomer within the scope of claim 17. The Examiner found that Berger describes a method of synthesizing chiral amines by enantioselective allylation of acylhydrazones to obtain *chiral monoacylhydrazines* (Final Act. 13). The Examiner found that Berger does not teach synthesizing a diacylhydrazines of Formula III as claimed. However, the Examiner found that Hormann '146 teaches that "diacylhydrazines could be obtained by reacting **[*34]** *monoacylhydrazines* [produced in accordance with Berger's method] with compounds having the formula B-CO-LG to form diacylhydrazines" of the claimed Formula III (*id.* at 14 (emphasis added)). The Examiner found that reacting the compound as described in Berger would result in a modified compound with a double-bond and an --OCH[3] group (*id.* at 15). However, the Examiner found it would have been obvious to have hydrogenated the double-bond and replace the --OCH[3] group with a --OA group to obtain a. compound within the scope of the claimed Formula III (*id.* at 15-16). The Examiner stated that the compounds obtained by this method would fall within the scope of the claims, where the genus includes RG-1.15830 (Ans. 32-33).

Appellants identified the steps outlined by the Examiner to hale obtained compounds within the scope of claim 3 (Appeal Br. 28). Appellants did not challenge the Examiner's finding that these steps would have been routine to carry out. Rather, Appellants contend the Examiner used hindsight in selecting the claimed structure as a roadmap to pick and choose from the prior art disclosures (*id.*). The picking and choosing contended by Appellants, as we **[*35]** understand it, is the choice of an enantiomerically enriched diacylhydrazines of the claims (*id.*).

Appellants state:

> Based on the pretext that "the prior art teaches improved insecticidal activity when using chiral diacylhydrazines" coupled with the improper selection of RG-115830 as a lead compound, the Office arrives a method of making the claimed diacylhydrazines having an ee of at least 95% by "simply retrac[ing] the path of the inventor with hindsight, discount[ing] the number and complexity of the alternatives, and conclud[ing] that the [method] was obvious." Ortho-McNeil ***Pharm.***, Inc. v. Mylan Labs., Inc., 520 F.3d 1358, 1364 (Fed. Cir. 2008).

Appeal Br. 29.

As already discussed, Zhang teaches that it "is not uncommon for one enantiomer to be active while the other is toxic in biological systems" (FF2), providing a reason to have made the different enantiomers in a racemate mixture. Hsu also teaches difference in properties between enantiomers (FF16), as does Wang, which teaches that enantiomers may differ in bioactivity and toxicity (FF17). Thus, there is Strong reasons to have made enantiomers of claim 3, including one of RG-115830. **[*36]** The Examiner did not use the claims as a road map to pick and choose a compound because Hormann '146 describes compounds within the scope of claim 3, albeit as racemates.

Appellants also argue that there are benchmark diacylhydrazine insecticides, including commercially relevant diacylhydrazine insecticides which are substituted directly on the nitrogen atom with a tert-butyl group. Appeal Br. 29. Based on these disclosures and those of Hsu, Appellants contend that "the prior art fairly suggests a preference for *teat-butyl* substitution on the diacylhydrazine nitrogen atom, and Appellant's diacylhydrazines are substituted by a secondary alkyl group on the nitrogen atom." *Id.* at 30.

Simply because there are known and commercialized diacylhydrazines does not mean that one of ordinary skill in the art would not developed alternatives. The fact that Hormann '146 and Hsu synthesized a large genus of compounds indicates that the skilled worker actively sought other biologically active diacylhydrazines, contrary to Appellants' contention. *See Peterson*, 315 F.3d at 1329-30 (Fed. Cir. 2003). Appellants did not provide evidence that the particular substitutions **[*37]** described in Hormann '146 had no, or even less, activity than those of the "commercially relevant" compounds referred to by Appellants. Moreover, "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." In re Mouttet, 686 F.3d 1322, 1334 (Fed. Cir. 2012).

Accordingly for the foregoing reasons, the obviousness rejection based on Berger of claims 3 and 17 is affirmed. Claims 20 and 57 were not argued separately and fall with claims 20 and 57. 37 C.F.R § 41.37(c)(1)(iv).

TIME PERIOD

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv).

AFFIRMED

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