United States Court of Appeals for the Federal Circuit

DAIICHI SANKYO COMPANY, LTD., AND DAIICHI SANKYO, INC.,
Plaintiffs/Counterclaim

Defendant-Appellees,

v.

MATRIX LABORATORIES, LTD., MYLAN INC., MYLAN LABORATORIES, INC., AND MYLAN PHARMACEUTICALS, INC.,
Defendants-Counterclaimant-Appellants.

2009-1511

Appeal from the United States District Court for the District of New Jersey in Case No. 06-CV-03462, Judge William J. Martini.

Decided: September 9, 2010

DOMINICK A. CONDE, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs/counterclaim defendant-appellees. With him on the brief were LISA B. PENSABENE and JOSHUA I. ROTHMAN. Of counsel on the brief were HENRY B. GUTMAN, ROBERT

A. BOURQUE and NOAH M. LEIBOWITZ, Simpson Thacher & Bartlett LLP, of New York, New York.

ROBERT L. BYER, Duane Morris LLP, of Pittsburgh, Pennsylvania, argued for defendants/counterclaimant-appellants. Of counsel on the brief were SHANNON M. BLOODWORTH, Perkins Coie LLP, of Washington, DC, and DAVID J. HARTH, The Law Office of David J. Harth, of Madison, Wisconsin. Of counsel was DAN L. BAGATELL, Perkins Coie Brown & Bain P.A., of Phoenix, Arizona.

Before LOURIE, FRIEDMAN, and LINN, *Circuit Judges*.

LOURIE, *Circuit Judge*.

Matrix Laboratories, Ltd., Mylan Inc., Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc. (collectively, "Mylan") appeal from the final decision of the United States District Court for the District of New Jersey sustaining the validity of U.S. Patent 5,616,599 ("the '599 patent") under 35 U.S.C. § 103. We affirm.

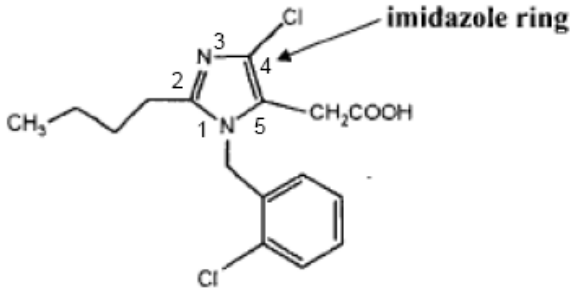
BACKGROUND

I.

Daiichi Sankyo Company, Ltd. and Daiichi Sankyo, Inc. (collectively, "Daiichi") own the '599 patent, which claims 1-biphenylmethylimidazole compounds and their use as angiotensin receptor blockers ("ARBs") for the treatment of high blood pressure. Claim 13 of the '599 patent covers the chemical compound olmesartan medoxomil, an ARB approved by the Food and Drug Administration ("FDA") and commercialized by Daiichi as the active ingredient in Benicar®, Benicar HCT®, and Azor®.

The invention of olmesartan medoxomil as an effective ARB built on years of research beginning in the

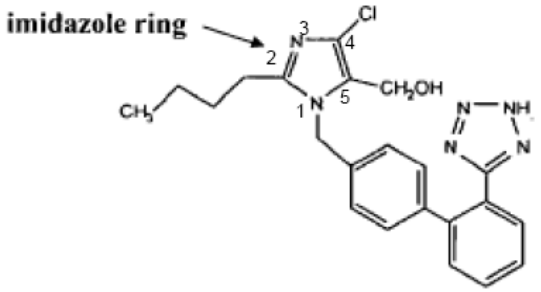
1970s, when scientists first came to appreciate the role of the angiotensin protein in controlling blood pressure. The first non-protein, small molecule ARBs were developed in the late 1970s and early 1980s by the Japanese pharmaceutical company Takeda Pharmaceutical Co. Ltd. ("Takeda"). These compounds each comprised an imidazole ring—a five-membered ring of the formula $C_3H_4N_2$—to which other chemical moieties were bonded at the 1-5-positions of the ring. One Takeda compound, S-8307, possessed a chlorophenyl group bonded through a methylene group at the 1-position, a butyl group (-C_4H_9) at the 2-position, a chlorine atom (-Cl) at the 4-position, and an acetic acid moiety (-CH_2COOH) at the 5-position. The chemical structure of S-8307 is pictured below with the ring's 1-position nitrogen positioned at the bottom of the ring.



S-8307
(Takeda)

The Takeda compounds, however, bound only weakly to the angiotensin receptor and thus were of little therapeutic value. Nevertheless, using Takeda's compounds as leads, scientists at E. I. du Pont de Nemours and Company ("DuPont") embarked on their own ARB research program with the aim of developing new compounds with

increased receptor-binding activity. DuPont's research led to the discovery of the first orally active ARB, known as losartan, which exhibited ten-fold greater binding affinity than the Takeda compounds. To obtain losartan, DuPont modified Takeda's S-8307 at the 1- and 5-positions of the imidazole ring: At the 1-position, DuPont added a second phenyl group with a tetrazole group attached, generating a biphenyltetrazole substituent. At the 5-position, DuPont replaced the acetic acid group with a hydroxymethyl group (-CH_2OH), which is metabolized to a carboxylic acid (-COOH) in the body. The chemical structure of losartan is depicted below.



LOSARTAN
(DuPont)

DuPont disclosed losartan in U.S. Patent 5,138,069 ("the '069 patent") along with more than four hundred structurally related ARBs. The '069 patent also discloses binding affinity data, measured as IC_{50} values,[1] for over two hundred compounds, including forty-two in losartan's biphenyltetrazole series. Chemists were able to use the

[1] The half maximal inhibitory concentration, or IC_{50}, represents the concentration of an inhibitor that is required for 50% inhibition of its target, and thus the effectiveness of an inhibitor. More specifically, a lower IC_{50} indicates a higher affinity binding.

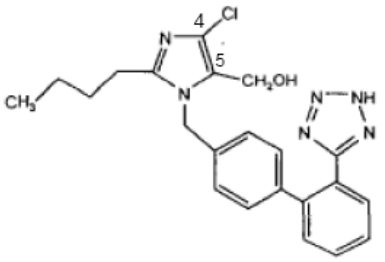
data disclosed in the '069 patent to uncover correlations between the compounds' structures and their binding affinities, called "structural-activity relationships" ("SARs"), which they could then use to guide the development of even more potent ARBs. For example, if the presence of a certain chemical moiety or type of chemical moiety at a given position correlates with an increase in binding affinity, chemists could attempt to use that chemical moiety or type of moiety in the next generation of ARBs, and they did.

Following losartan's success, over twenty different pharmaceutical companies, including Daiichi, established research programs to develop the next generation of ARBs. Daiichi's program resulted in the synthesis of olmesartan, the active metabolite of olmesartan medoxomil. Like losartan, olmesartan consists of an imidazole ring containing a biphenyltetrazole substituent at the 1-position and an alkyl group (propyl rather than butyl) at the 2-position. At the 4-position, however, olmesartan replaced losartan's lipophilic, or fat-loving, chlorine atom with its opposite, a hydrophilic, or water-loving, hydroxyisopropyl group ($-C(CH_3)_2OH$).[2] Of the compounds disclosed in DuPont's '069 patent, the vast majority contain a lipophilic group at the ring's 4-position. One compound with a hydrophilic group is losartan's regioisomer,[3] Example 118, in which the 4- and 5-positions on the imida-

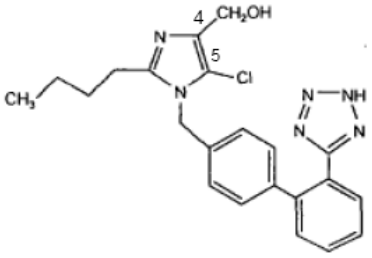
[2] When one speaks of replacing one group with another, it is understood that the "replacement" is not accomplished merely by writing it on paper and that an actual change from one group to another more often occurs by a new synthesis using different starting materials, *i.e.*, a chlorine atom is not directly replaced with a hydroxyisopropyl group.

[3] A regioisomer of another compound is one in which substituents around a ring are the same, but varied in position.

zole ring are reversed. The transposition results in a compound with a chlorine atom at the 5-position and a hydrophilic hydroxymethyl group (-CH_2OH) at the 4-position, as shown below.

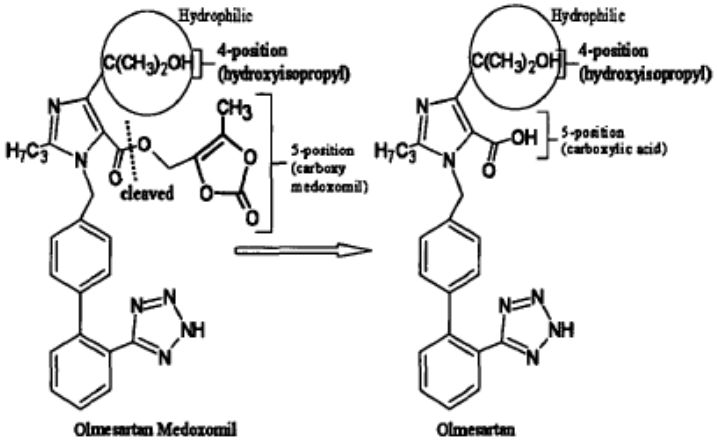


LOSARTAN

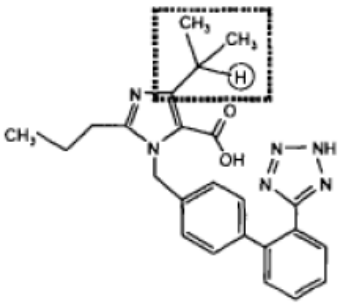


EXAMPLE 118

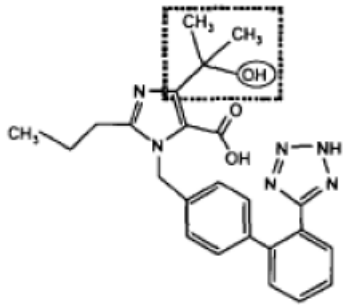
Olmesartan medoxomil also differs from losartan at the 5-position. Daiichi replaced losartan's hydroxymethyl group with a carboxy group masked by a medoxomil prodrug substituent to improve oral absorption. Like the hydroxymethyl group, the medoxomil moiety is metabolized to the carboxylic acid in the body. The structures of olmesartan medoxomil and olmesartan are depicted below.



Other second-generation ARBs, all prior art to olmesartan medoxomil, include DuPont's DuP 532, in which losartan's chlorine at the 4-position is replaced with multiple lipophilic fluorine atoms ($-C_2F_5$), and six compounds disclosed in DuPont's U.S. Patent 5,137,902 ("the '902 patent"), each of which has a more lipophilic alkyl group at the 4-position. The ARBs disclosed in DuPont's '902 patent ("the '902 compounds" or "the '902 ARBs") are the closest structurally to olmesartan, with Example 6 differing from olmesartan by only a single oxygen atom at the 4-position, as depicted below



'902 Example 6



Olmesartan

Other second-generation ARBs differ more significantly from losartan by not containing an imidazole ring, including Merck & Co., Inc.'s L-158,809 compound, Ciba-Geigy Corp.'s valsartan, and Eisai Inc.'s E-4177 compound.

II.

Mylan filed multiple Abbreviated New Drug Applications ("ANDAs") with Paragraph IV certifications under the Hatch-Waxman Act, 21 U.S.C. § 355, challenging the '599 patent and seeking FDA approval to manufacture generic olmesartan medoxomil in various dosages and combinations. Daiichi responded by filing suit against Mylan for patent infringement in the United States District Court for the District of New Jersey. The parties stipulated to infringement of claim 13, leaving only Mylan's counterclaim that claim 13 would have been obvious in light of (1) the second-generation ARBs in DuPont's '902 patent, which Mylan alleged one of skill in the art would have been motivated to select as lead compounds; (2) Example 118, losartan's regioisomer, in DuPont's '069 patent, which Mylan alleged would have motivated one of skill in the art to modify the '902 compounds' lipophilic alkyl groups at the 4-position with olmesartan's hydro-

philic hydroxyalkyl group; and (3) the well-known use of medoxomil as a prodrug.

After a ten-day bench trial, the district court held, in a comprehensive and well-reasoned opinion, that claim 13 of the '599 patent was not invalid as obvious. *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359 (D.N.J. 2009). The court determined that Mylan had failed to show by clear and convincing evidence that one skilled in the art would have chosen the '902 ARBs as lead compounds over other better-studied ARBs with greater potency and thus had failed to establish a *prima facie* case of obviousness. *Id.* at 376-77. The district court went on to find that, even assuming that Mylan had shown the '902 ARBs to be leads, the structure of the '902 compounds differed significantly from olmesartan medoxomil, *id.* at 377-78, and that, even assuming structural similarity, Mylan had failed to prove that one of skill in the art would have been motivated to modify the 4- and 5-positions of the '902 ARBs to obtain olmesartan medoxomil, *id.* at 378-81. Regarding the 4-position, the court found that the emphasis on lipophilicity in both the '069 patent and the second-generation ARBs taught away from the use of a hydrophilic group at the 4-position and from any expectation that the use of a hydrophilic group would generate an ARB with significantly improved biological properties. *Id.* at 370-75, 378-80. Regarding the 5-position, the court found that converting olmesartan into a prodrug was a disfavored and unpredictable approach and that medoxomil was a disfavored prodrug. *Id.* at 380.

Finally, the district court concluded that even if Mylan had established a *prima facie* case of obviousness, secondary considerations counseled against a finding of obviousness. *Id.* at 381. Specifically, the court found evidence of unexpected results in olmesartan medoxomil's enhanced potency and other favorable biological proper-

ties. *Id.* at 382-84. The court also found evidence of commercial success based on the significant market penetration of Benicar® despite being the seventh ARB on the market and despite Daiichi spending roughly the same amount in marketing as its competitors. *Id.* at 384-86.

On August 6, 2009, the district court entered final judgment and permanently enjoined Mylan's commercialization of olmesartan medoxomil until the expiration of the '599 patent. Mylan appealed. We have jurisdiction pursuant to 19 U.S.C. § 1295(a)(1).

DISCUSSION

Under the Patent Act, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). While the ultimate determination of obviousness under § 103 is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). After a bench trial, we review the district court's conclusions of law *de novo* and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is clearly erroneous if, despite some supporting evidence, a reviewing court is left with the definite and firm conviction that a mistake has been

made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

When a patent claims a chemical compound, a *prima facie* case of obviousness under the third *Graham* factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) ("This court . . . reaffirms that 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."); *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. *Eisai*, 533 F.3d at 1357; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the inquiry after *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the motivation to select and modify a lead compound need not be explicit in the art. *Eisai*, 533 F.3d at 1357; *Takeda*, 492 F.3d at 1356-57.

Mylan challenges, as it must to prevail, every step in the district court's decision holding that Mylan failed to establish its *prima facie* case that olmesartan medoxomil would have been obvious in light of the prior art. Specifically, Mylan challenges the district court's finding that one of skill in the art would not have selected the six ARBs in DuPont's '902 patent as lead compounds, pointing to evidence that the '902 compounds are undisputedly

the closest prior art. Mylan also challenges the court's finding that the '902 ARBs are not structurally similar to olmesartan medoxomil, arguing that one of the '902 compounds differs from olmesartan by only a single oxygen atom. Mylan also argues that the district court erred in finding no motivation to modify the '902 compounds at the 4- and 5-positions to arrive at olmesartan medoxomil when the '069 patent specifically taught a compound with a hydroxyalkyl group at the 4-position and the art taught medoxomil as a well-known prodrug for improving oral activity. Finally, Mylan contends that, contrary to the district court's finding, one of skill in the art would have had a reasonable expectation that modifying the '902 compounds to obtain olmesartan medoxomil would result in a similarly effective ARB.

In response, Daiichi defends the factual findings underlying the district court's determination that claim 13 of the '599 patent was not invalid as obvious. Daiichi first argues that the district court correctly found that one of skill in the art would not have been motivated to select the '902 ARBs as lead compounds over other more potent and better-studied prior art ARBs. Daiichi next asserts that the district court correctly found no motivation to modify the '902 compounds to create olmesartan medoxomil based on the lack of structural similarity between the '902 ARBs and olmesartan medoxomil, the existence of thousands of possible modifications, the illogic of selecting the '902 compounds as leads only to reject their distinguishing characteristic of increased lipophilicity at the 4-position, the fact that the prior art taught away from such an alteration at the 4-position, and the unpredictability associated with the use of a prodrug in general and medoxomil in particular. Finally, according to Daiichi, the district court correctly found no reasonable expecta-

tion that the proposed modifications would lead to an ARB with significantly improved activity over losartan.

We agree with Daiichi that the district court did not err in holding that Mylan failed to establish a *prima facie* case of obviousness. Specifically, we agree that Mylan failed to show that one of ordinary skill in the art would have been motivated to select the '902 ARBs as lead compounds or, even if they had, that the skilled artisan would have been motivated to modify the '902 compounds to synthesize olmesartan medoxomil, the claimed invention. We address each in turn.

I. Selection of a Lead Compound

In rejecting the '902 ARBs as lead compounds, the district court accepted as true all of Mylan's evidence on the '902 compounds, including that they represented a continuation of DuPont's work on the ARBs disclosed in the '069 patent, including losartan, and thus could take advantage of the '069 patent's SAR data, and that the preferred '902 compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" with "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." *Daiichi Sankyo*, 670 F. Supp. 2d at 376 (alternations in original). Nevertheless, the court found that a medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over other second-generation ARBs, including L-158,809, DuP 532, the Eisai compounds, and valsartan, because many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs. Specifically, the court found that L-158,809 had 180 times, Example 7 of the Eisai compounds had 100 times, and DuP 532 had seven times the potency of losartan. *Id.* The court also found that while the '902 patent disclosed

in vivo oral activity, the prior art included not only data on oral activity for all but the Eisai compounds, but also data on the binding affinity and intravenous activity for L-158,809, the Eisai compounds, DuP 532, and valsartan as well as selectivity data for L-158,809 and DuP 532. *Id.* Finally, the court found that DuP 532, which shared losartan's imidazole-biphenyltetrazole backbone, could also benefit from the '069 patent's SAR data. *Id.* We see no clear error in the court's findings.

Mylan argues that because the '902 ARBs are undisputedly the closest prior art, that "should have been dispositive of the lead compound issue." Appellant Principal Br. 25. That argument runs contrary to our case law. In *Takeda*, we upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound, compound b, as the lead compound in light of other compounds with more favorable characteristics. 492 F.3d at 1357-59. We reached the same result in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1377-79 (Fed. Cir. 2006). These cases illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention. *See Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Accordingly, proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. *See Eli Lilly*, 471 F.3d at 1377-

79. Potent and promising activity in the prior art trumps mere structural relationships.

Mylan further faults the district court for not following this court's "clarification that a 'lead compound' analysis does not require identification of a single, best, compound as a starting point" but "the prior art may point to more than a 'single lead compound for further development efforts.'" Appellant Principal Br. 24 (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). But that misinterprets the district court's decision. As described above, the district court selected multiple compounds as leads, just not the compounds disclosed in the '902 patent. *Daiichi*, 670 F. Supp. 2d at 376. Contradicting itself, Mylan also faults the district court for selecting only five potential leads and for not including the '902 compounds among that finite number. While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, *see Altana Pharma*, 566 F.3d at 1008, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art. Here, the district court did not commit error, let alone clear error, in finding that Mylan failed to meet that burden.

II. Motivation to Modify

The district court next found that, even accepting the '902 compounds as lead compounds, one of skill in the art would not have been motivated to modify the ARBs disclosed in the '902 patent to obtain olmesartan medoxomil. Specifically, the court found that the prior art as a whole taught away from the use of a hydrophilic substitute at the 4-position of the imidazole ring, relying on, *inter alia*,

the structural-activity relationship ("SAR") data in the '069 patent and the use of lipophilic groups at the 4-position in other second-generation compounds, including DuPont's '902 compounds. *Daiichi*, 670 F. Supp. 2d at 369-75. Accordingly, the district court also found that the prior art provided no motivation to modify the '902 compounds' lipophilic alkyls at the 4-position to the hydrophilic hydroxyisopropyl group of olmesartan. *Id.* at 378-80. Again we find no error in the district court's findings.

The '069 patent reveals a clear preference for lipophilic groups at the 4-position of the imidazole ring. The vast majority of the '069 compounds contain a lipophilic group at this position, as do twenty-seven of the thirty most active compounds, with two containing a neutral group and only one, Example 342, containing a hydrophilic group. J.A. 13717. This preference extends to the forty-two compounds in losartan's biphenyltetrazole series. Again, the vast majority, thirty-six out of forty-two compounds, have a lipophilic group at the 4-position and only four compounds, Examples 342, 329, 118, and 335, have a hydrophilic group. *Id.* at 7715. The few compounds with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds, which are the essence of what the '069 patent teaches.

Three subseries analyses comparing the binding affinity of '069 patent compounds that vary only at the imidazole ring's 4-position confirm the preference for lipophilicity at the 4-position. In the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a hydroxymethyl group at the 5-position (1) three out of four compounds with a lipophilic group at the 4-position exhibit higher affinity binding, measured as a lower IC_{50}, than Example 334 with a neutral group, and (2) all four compounds with a lipophilic group exhibit higher affinity binding than

Example 335 with a hydrophilic group. Specifically, Examples 124F, 124D, 124K, and 113 with lipophilic groups at the 4-position have IC_{50} values of 0.001 μM, 0.006 μM, 0.013 μM, and 0.020 μM, respectively, compared to an IC_{50} of 0.015 μM for Example 334, which has the highest binding affinity of any compound with a non-lipophilic group, and an IC_{50} of 0.26 μM for Example 335. *Id.* at 13721.

Similarly, in the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a carboxylic acid at the 5-position, two out of three compounds with a lipophilic group at the 4-position exhibit higher affinity binding than Example 329 with a hydrophilic group. Specifically, Examples 265C (DuPont's DuP 532) and 251A have IC_{50} values of 0.003 μM and 0.045 μM compared to an IC_{50} of 0.076 for Example 329. *Id.* at 13720. Finally, Example 342, described above as the compound with the highest binding affinity of any compound with a hydrophilic group at the 4-position, has a lower binding affinity, higher IC_{50}, than Example 140J, which differs only by the substitution of a lipophilic group at the 4-position. *Id.* at 13725. Thus, the compounds in the prior art, including the parties' proposed lead compounds, favor lipophilic 4-substitutents rather than the 4-hydrophilic group of olmesartan medoxomil.

An analysis of regioisomer pairs in which the 4- and 5-positions are transposed provides even further confirmation. For all eight regioisomer pairs, the regioisomer with a lipophilic group at the 4-position has higher binding affinity than the regioisomer with a hydrophilic group at that position. *Id.* at 13713-16. In the 6155 series, for example, two compounds with lipophilic chlorine atoms at the 4-position exhibit ten-fold and 100-fold better binding than compounds with a hydrophilic acetic acid or hy-

droxymethyl group, respectively. *Id.* at 13713. And in the biphenyltetrazole series, losartan with a chlorine at the 4-position has two-fold higher binding affinity than its regioisomer, Example 118, with a hydrophilic hydroxymethyl group. *Id.* at 13716.

DuPont's second-generation ARBs repeat and enhance the preference for lipophilicity at the 4-position. Specifically, DuPont's DuP 532 replaces losartan's chlorine atom with a more lipophilic multiple fluorine group ($-C_2F_5$), and the six '902 compounds replace the chlorine with more lipophilic alkyl groups. No other second-generation ARB but olmesartan medoxomil has a hydrophilic group at the 4-position. *Id.* at 13722. Altogether, the '069 patent's SAR data and the structure of other second-generation ARBs counter any notion that one of skill in the art would have been motivated to modify the '902 compounds' lipophilic alkyl groups to a hydrophilic group. Such a holding would have been based on hindsight.

Mylan argues that the motivation to modify comes directly from the '069 patent and specifically from Example 118, losartan's regioisomer, with its hydrophilic hydroxymethyl group at the 4-position. According to Mylan, the parties' experts agreed that Example 118 is one of the more potent and important of the compounds disclosed in the '069 patent, and thus, Mylan argues, although Example 118 is slightly less potent than losartan, it would have motivated one of skill in the art to alter the '902 compounds' alkyl groups to a hydrophilic group. Alternatively, Mylan argues, even without the benefit of Example 118, one of skill in the art would have been motivated to make the "minor" modification of hydroxylation of the

'902 compounds' alkyls to produce a hydroxyisopropyl.[4] We disagree.

First, the SAR data in the '069 patent, described in detail above, contradict Mylan's arguments. Example 118 may be one of the more potent biphenyltetrazole compounds disclosed in the '069 patent, but it is one of only four to contain a hydrophilic group at the 4-position and one of only six to have a non-lipophilic group at that position. Furthermore its regioisomer, losartan, displays greater binding affinity as do all the disclosed regioisomers with a lipophilic group compared to a hydrophilic group at the 4-position. And while the '069 patent's SAR data do not make available a subseries analysis for Example 118, all available subseries, as described above, demonstrate a clear preference for lipophilic groups over hydrophilic ones.

Second, Mylan's argument relies on first selecting the '902 compounds, which improved on losartan by using even more lipophilic alkyl groups at the 4-position, only to reject that very feature to obtain olmesartan medoxomil. *See Eisai*, 533 F.3d at 1358 (affirming a holding of non-obviousness based in part on a finding that the record "show[ed] no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature . . . that gave [it an] advantageous property"). As the district court in this case put it, "a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position." *Daiichi*, 670 F. Supp. 2d at 379.

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[4] In fact, a difference of only a single oxygen atom between Example 6 of the '902 patent and olmesartan, as noted by Mylan, is of greater significance than it superficially appears, as it is the difference between functional groups, specifically an isopropyl and a hydroxyisopropyl.

Finally, even crediting Mylan's argument that the '069 patent does not teach away from a hydrophilic group at the 4-position, the '069 patent simply does not provide a reason to make such a modification. We thus affirm the district court's decision holding that one of skill in the art would not have been motivated to modify the '902 compounds at the 4-position to obtain a compound with a hydrophilic hydroxyalkyl group.

Because we affirm the district court's findings that Mylan failed to establish either that one of skill in the art would have selected the '902 ARBs as leads or that one of skill in the art would have modified the '902 ARBs at the 4-position of the imidazole ring to obtain olmesartan medoxomil, we need not address the district court's alternative grounds for holding that Mylan failed to establish a *prima facie* case of obviousness or the court's findings on secondary considerations.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision holding that claim 13 of the '599 patent was not shown to be invalid as obvious.

AFFIRMED