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Federal Circuit Affirms PTAB Lead Compound Analysis Upholding Vimpat Lacosamide Patent

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The Federal Circuit decision in *Mylan Pharmaceuticals, Inc. v. Research Corporation Technologies, Inc.*, highlights the difficulty of challenging a patent directed to a new chemical entity. The court affirmed the decision of the USPTO Patent Trial and Appeal Board (PTAB) that upheld the validity of RCT's Vimpat lacosamide patent, which is approved for the treatment of epilepsy. The court considered the arguments that had been made for and against patentability under the "lead compound analysis" framework, and determined that the PTAB decision was supported by substantial evidence.

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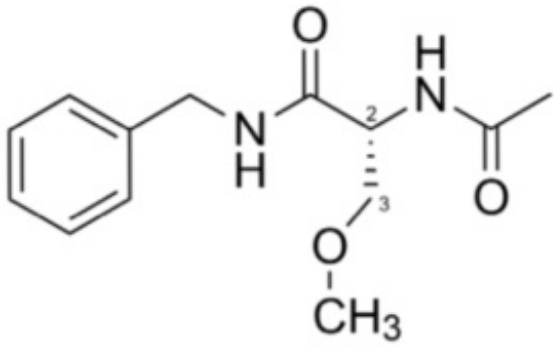
The Vimpat Lacosamide Patent At Issue

The patent at issue was RCT's RE38551, which is the sole patent listed in the Orange Book for Vimpat® (lacosamide), which is used to treat seizures. The claims addressed in the Federal Circuit decision were claims 8-13, directed to the compound lacosamide:

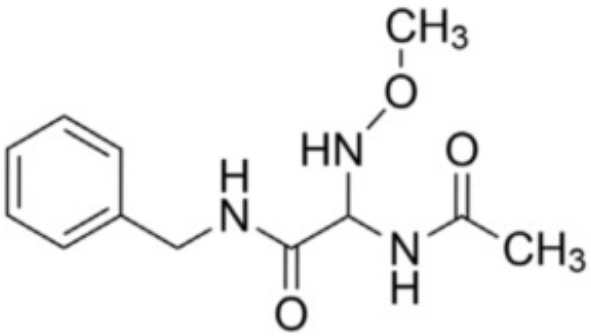


"compound 31" of the Kohn reference:

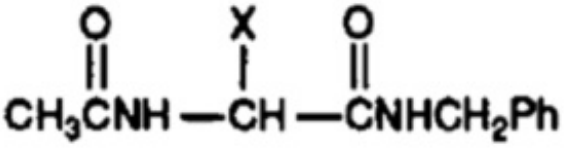
The IPR Proceeding

The case originated with an *Inter Partes* Review (IPR) proceeding initiated by Argentum Pharmaceuticals LLC. After the PTAB issued an institution decision, Mylan, Breckenridge Pharmaceutical, Inc., and Alembic Pharmaceuticals Ltd. filed parallel IPR petitions and motions to join the Argentum proceeding, which eventually were granted. Only Mylan, Breckenridge, and Alembic appealed the PTAB's final written decision.

The arguments for invalidity were based on a lead compound analysis starting with the following "lead" compound, which was



As summarized in the Federal Circuit decision, Kohn "discloses a series of functionalized amino acids ("FAAs") with anticonvulsant activity" based on the following structure.



As also summarized in the Federal Circuit decision, Kohn "evaluated the potency of the compounds in mice, reporting for each the effective dosage for 50 percent of the tested population (ED50)." From those studies, Kohn found that compound 31 had the highest efficacy.

The asserted motivation to modify compound 31 to arrive at lacosamide was said to be provided by Silverman, which discloses general approaches to drug design, including modifications based on "bioisosterism" in order to attenuate toxicity. As explained in the decision, "bioisosteres" are "substituents or groups that have chemical or physical similarities, and which produce broadly similar biological properties." Silverman discloses "the following compounds as classical isosteres:"

–CH2–, –NH–, –O–, –S–, and –Se–

For its institution decision, the PTAB determined that Argentum had satisfied its burden of showing that compound 31 would have been selected as a lead compound, and that a person of ordinary skill in the art would have been motivated to replace the amino group (–NH–) in compound 31 with a methylene group to arrive at lacosamide.

In its final decision, the PTAB again accepted that compound 31 would have been selected as a lead compound, but credited RCT's evidence that "converting the methoxyamino group would have been viewed as undesirable." The PTAB noted that compounds in Kohn "without a methoxyamino or nitrogen-containing moiety at the α-carbon had reduced activity" and "credited evidence suggesting that an ordinary artisan would have understood the methoxyamino moiety to confer significant activity to the compound and that substitution of nitrogen for carbon would have led to a significantly different conformation and biological activity." With regard to Silverman, the PTAB noted "a lack of 'specific evidence suggesting an ordinary artisan would have understood that modifying the methoxyamino group of Kohn 1991's compound 31 would have reduced that compound's toxicity." Thus, the PTAB concluded that the claims had not been shown to be obvious by a preponderance of the evidence.

The Federal Circuit Decision

The Federal Circuit decision was authored by Judge Lourie and joined by Judges Bryson and Wallach.

The Federal Circuit reviewed the arguments on appeal, and identified the following among the "substantial evidence" supporting the PTAB decision:

- Even if a person of skill in the art would have been motivated to modify compound 31, the record evidence suggests that compounds without a methoxyamino or nitrogen-containing group at the α-carbon had reduced activity.
- The asserted modification of compound 31 would have resulted in a different conformation, which Kohn indicated would affect biological activity.
- "[T]he record does not indicate why bioisosterism would have been used to modify compound 31 in particular, which already had a high potency and low toxicity, and why methylene was a natural isostere of methoxyamino."

Thus, the court affirmed the PTAB decision.

Lead Compound Analysis

This decision highlights the challenges of invalidating a patent under a lead compound analysis framework. Not only must a prior art lead compound be identified and a rationale for the asserted modification be found in the prior art, but the rationale must be shown to be relevant to the specific lead compound at issue.

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