

Lead Compound Obviousness Analysis

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Customer Partnership

United States Patent and Trademark Office



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Outline

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- BPAI Decisions
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- Thank you to Jane Dai and Andrew Morrell

What is Lead Compound Analysis?

- Obviousness analysis based on structural similarity between a known compound or compounds and the claimed compounds
 - Homologs
 - Analogues
 - Isomers

Graham v. John Deere (1966)

- The Three-Factor Test:
 - The scope and content of the prior art
 - The level of ordinary skill in the art
 - The differences between the prior art and the claimed invention
- Secondary Considerations
 - Commercial success, long-felt but unsolved needs, failure of others, and unexpected results

KSR v. Teleflex (2007)

- An “expansive and flexible approach”
 - “When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art 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.”

550 U.S. 398, 419 (2007)

MPEP

- MPEP 2144.09 Close Structural Similarity Between Chemical Compounds (Homologs, Analogues, Isomers)
 - Rejection based on close structural similarity is founded on the expectation that compounds similar in structure will have similar properties
 - A *prima facie* case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities
 - Homology and isomerism are facts which must be considered with all other relevant facts in determining obviousness
 - Homology should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed "as a whole." *In re Langer*, 465 F.2d 896 (CCPA 1972)
 - Presence of a true homologous or isomeric relationship is not controlling
 - Presumption of obviousness based on structural similarity is overcome where there is no reasonable expectation of similar properties

PTO Guidelines for Lead Compounds

- Examination Guidelines Update: Developments in the Obviousness Inquiry After *KSR v. Teleflex*
- “In the chemical arts, the cases involving so-called ‘lead compounds’ form an important subgroup of the obviousness cases that are based on substitution. The Federal Circuit has had a number of opportunities since the KSR decision to discuss the circumstances under which it would have been obvious to modify a known compound to arrive at a claimed compound. The following cases explore the selection of a lead compound, the need to provide a reason for any proposed modification, and the predictability of the result.” 75 FR 53644, 53651 (Sept. 1 2010).

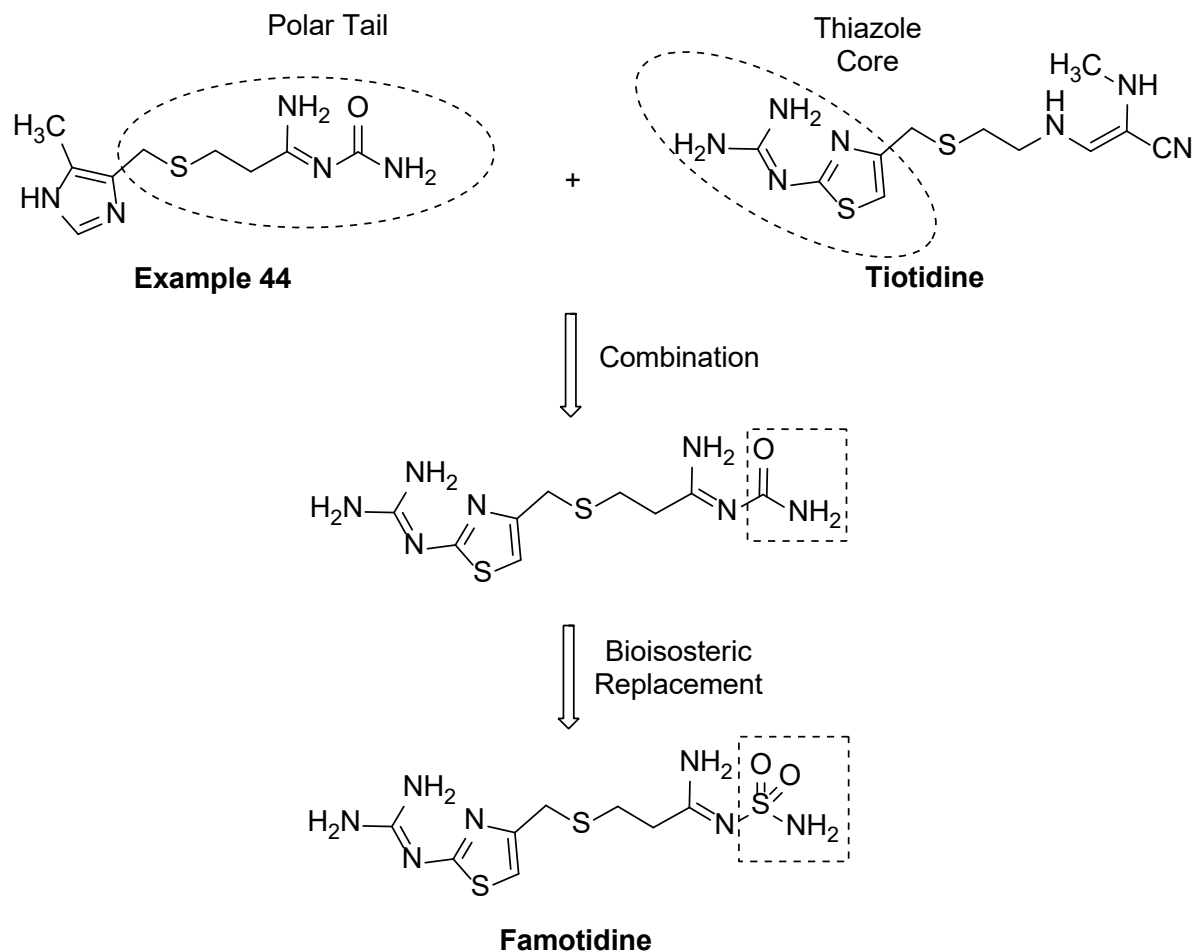
In Re Dillon (1990)

- The claimed fuel compositions containing tetra-orthoesters were obvious over fuel compositions containing tri-orthoesters
 - Prior art disclosed use of both tetra-orthoesters and tri-orthoesters in fuels
 - Close structural similarity between tetra-orthoesters and tri-orthoesters
 - “This court, in reconsidering this issue en banc, 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, and that the burden (an opportunity) then falls on an applicant to rebut that prima facie case.”
 - “There is no question that all evidence of the properties of the claimed compositions and the prior art must be considered in determining the ultimate question of patentability, but it is also clear that the discovery that a claimed composition possesses a property not disclosed for the prior art subject matter, does not by itself defeat a prima facie case.”

Yamanouchi v. Danbury (2000)

- The claimed compound Famotidine, an H₂ antagonist for treating heartburn and ulcers, was nonobvious over prior art compounds Example 44 and Tiotidine:
 - No motivation for selecting Example 44 as a lead compound.
 - No motivation to combine the polar tail of Example 44 with the substituted heterocycle of Tiotidine, then to substitute the carbamoyl with a sulfamoyl.

Yamanouchi v. Danbury (2000)



Yamanouchi v. Danbury (2000)

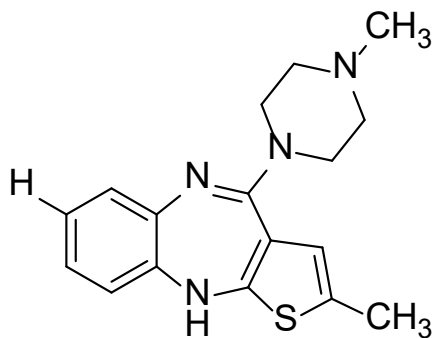
- Why is Famotidine not obvious?
 - Benchmark compound at time of invention: Cimetidine
 - Example 44 activity only 3x Cimetidine
 - Other potential lead compounds had activities up to 10x Cimetidine
 - Insufficient reason to select Example 44 as lead
 - “At the outset, Danbury did not show the required motivation for selecting Example 44 as a lead compound.”
 - No reason to pursue the particular order of manipulation.
 - “Danbury also does not show the motivation to combine the polar tail of example 44 with the substituted heterocycle of tiotidine, then to substitute the carbamoyl with a sulfamoyl.”
 - Expected activity of Famotidine was only 1/165 Cimetidine
 - No reasonable expectation of success.
- “For a chemical compound, a *prima facie* case of obviousness requires ‘structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.’” (citing to *Dillon*).
- “Because Danbury did not show even a *prima facie* case for obviousness, this court has considered, but need not separately address, the strong objective evidence of non-obviousness.”

Eli Lilly v. Zenith (2006)

- The claimed compound olanzapine, a member of the thienobenzodiazepines family for treating schizophrenia, was nonobvious over three prior art compounds in the same family – even though:
 - Flumezapine and ethyl flumezapine differ from olanzapine by the presence of fluorine atom on the benzene ring instead of a hydrogen atom.
 - Ethyl flumezapine and ethyl olanzapine differ from olanzapine by the presence of ethyl group on thiophene ring instead of a methyl group.

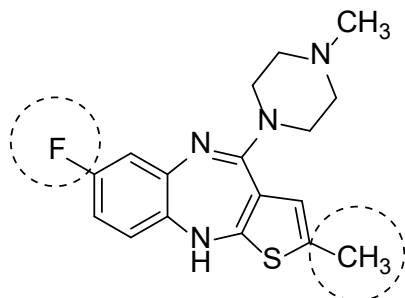
Eli Lilly v. Zenith (2006)

Claims

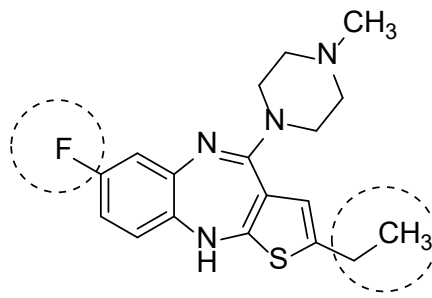


Olanzapine

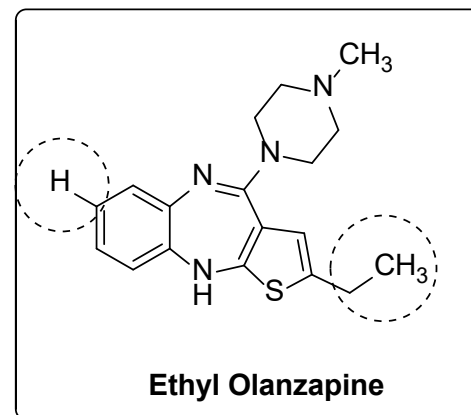
Prior Art



Flumezapine



Ethyl Flumezapine



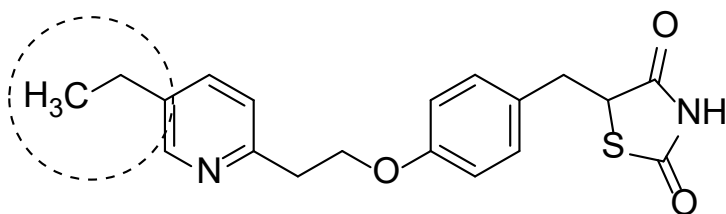
Ethyl Olanzapine

Eli Lilly v. Zenith (2006)

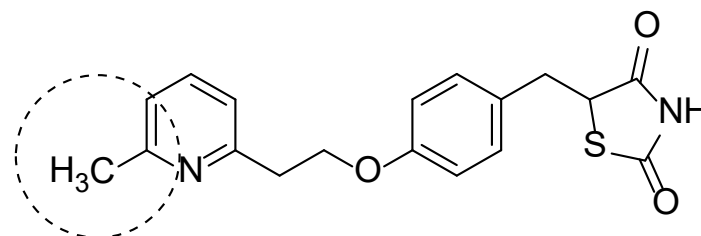
- Why is olanzapine not obvious?
 - Insufficient reason to select ethyl olanzapine as lead
 - Lacked the preferred halogen substituent
 - No biological data to support selecting ethyl olanzapine as lead
 - Ethyl flumezapine said to be “particularly active.”
 - No reason to modify ethyl olanzapine by replacing ethyl with methyl
 - If ethyl olanzapine had been selected as lead, then prior art taught in direction of replacing hydrogen with fluorine (to make ethyl flumezapine)
 - Even though olanzapine is adjacent homolog of ethyl olanzapine, “patentability for a chemical compound does not depend only on structural similarity. . . . This court will not ignore a relevant property of a compound in the obviousness calculus.”
 - No reasonable expectation of success
 - Olanzapine lacks halogen substituent.
- “For a chemical compound, a prima facie case of obviousness requires ‘structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.’” (citing to *Dillon*).

Takeda v. Alphapharm (2007)

- The claimed compound Pioglitazone, the active ingredient in Takeda's Type 2 anti-diabetic drug Actos®, was nonobvious over the prior art Compound B:
 - Compound B differs from Pioglitazone by having a 6-position methyl substituent while Pioglitazone has a 5-position ethyl substituent on the pyridine ring.



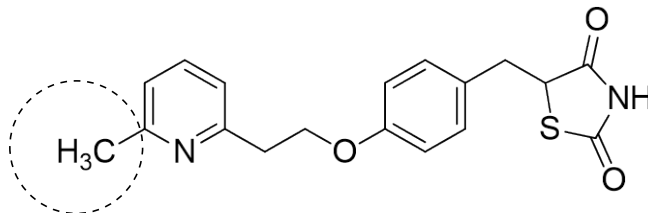
Pioglitazone



Compound B

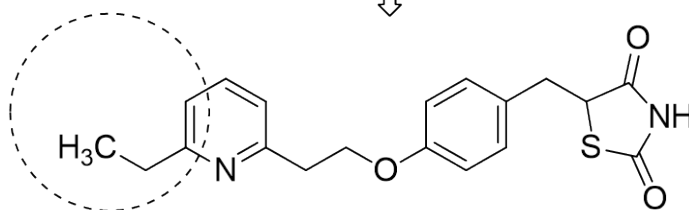
Takeda v. Alphapharm (2007)

Prior art

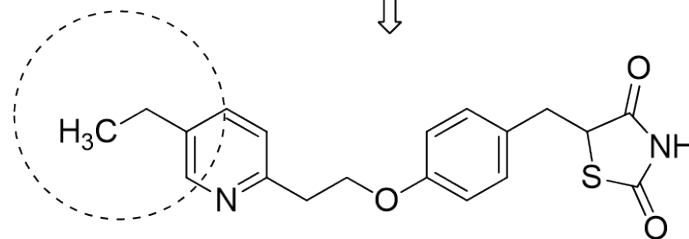


Compound B

Homologation



Ringwalking



Claims

Pioglitazone

Takeda v. Alphapharm (2007)

- Why is Pioglitazone not obvious?
 - No reason to select Compound B as lead
 - One prior art reference (Sodha II) identified three specific compounds having the most biological activity (not including Compound B), and singled out Compound B for its notable side effects.
 - No reason to modify and no reasonable expectation of success
 - Nothing in the prior art to provide a reasonable expectation that transforming Compound B's methyl substituent into an ethyl substituent, or changing the positions of a substituent on a pyridyl ring would reduce or eliminate Compound B's negative side effects.
- “We have held 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.’” (citing to *Dillon*).
- “Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound. We agree with Takeda and the district court that Alphapharm failed to make that showing here.”

Takeda v. Alphapharm (2007)

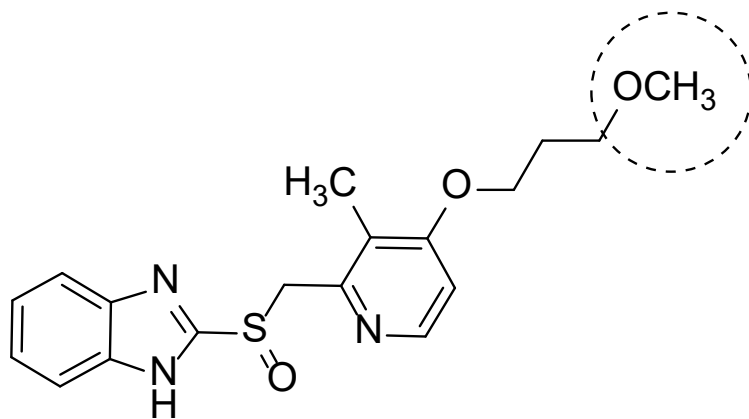
- PTO Guidelines:
 - “The *Takeda* case brings together the concept of a ‘lead compound’ and the obvious-to-try argument.”
 - Obvious to try rationale does not apply: “In *Takeda*, there was a recognized need for treatment of diabetes. However, there was no finite number of identified, predictable solutions to the recognized need, and no reasonable expectation of success.”
 - Teaching Point: “A claimed compound would not have been obvious where it was not obvious to try to obtain it from a broad range of compounds, any one of which could have been selected as the lead compound for further investigation, and the prior art taught away from using a particular lead compound, and there was no predictability or reasonable expectation of success in making the particular modifications necessary to transform the lead compound into the claimed compound.”

Eisai v. Dr. Reddy's (2008)

- The claimed compound rabeprazole, a proton pump inhibitor for treating stomach ulcers and related disorders, was nonobvious over the prior art references, even though –
 - The prior art compound lansoprazole shared a common core structure with rabeprazole and was useful for the same indications.
 - Lansoprazole differed from rabeprazole only in that it had a trifluoroethoxy substituent in place of a methoxypropoxy substituent, and therefore was suitable as a lead compound.

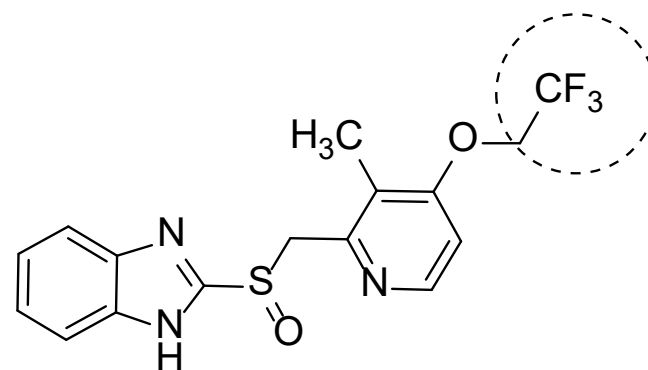
Eisai v. Dr. Reddy's (2008)

Claims



Rabeprazole

Prior Art



Lansoprazole

Eisai v. Dr. Reddy's (2008)

- Why was the claimed compound rabeprazole nonobvious?
 - Lansoprazole was a suitable lead compound.
 - 20x superior to omeprazole for anti-ulcer activity
 - Insufficient reason/no expectation of success for modifying lansoprazole
 - The prior art created the expectation that rabeprazole would be less useful than lansoprazole.
 - Modification would have reduced lipophilicity, a known advantageous property for such compounds.

Eisai v. Dr. Reddy's (2008)

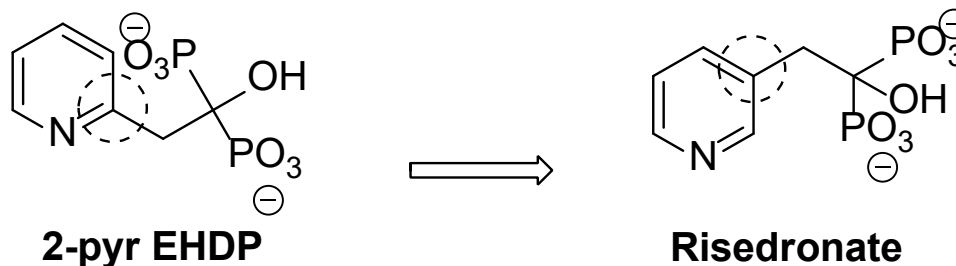
- “The Supreme Court’s analysis in *KSR* thus relies on several assumptions about the prior art landscape.”
 - “First, *KSR* assumes a starting reference point or points in the art . . . from which a skilled artisan might identify a problem and pursue potential solutions.”
 - “Second, *KSR* presupposes that the record . . . would give some reasons . . . to make particular modifications to achieve the claimed compound.”
 - “Third, the Supreme Court’s analysis in *KSR* presumes that the record . . . would supply some reasons for narrowing the prior art universe to a ‘finite number of identified, predictable solutions[.]’”
- “Where, as here, the patent at issue claims a chemical compound, the analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds.” [citing to *Dillon* and *Eli Lilly*; also quoting *Dillon*]
- “In other words, post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with a reasoned identification of a lead compound.”
 - No requirement for selection of single lead compound

Eisai v. Dr. Reddy's (2008)

- PTO Guidelines:
 - Teaching point: “A claimed compound would not have been obvious where there was no reason to modify the closest prior art lead compound to obtain the claimed compound and the prior art taught that modifying the lead compound would destroy its advantageous property. Any known compound may serve as a lead compound when there is some reason for starting with that lead compound and modifying it to obtain the claimed compound.”
 - “Thus, Office personnel should recognize that a proper obviousness rejection of a claimed compound that is useful as a drug might be made beginning with an inactive compound, if, for example, the reasons for modifying a prior art compound to arrive at the claimed compound have nothing to do with pharmaceutical activity. . . . However, there must be some reason for starting with the lead compound other than the mere fact that the ‘lead compound’ merely exists.”

P&G v. Teva (2009)

- The claimed compound risedronate, the active ingredient in the drug Actonel® for treatment of osteoporosis, was nonobvious over the prior art 2-pyr EHDP, even though –
 - The only structural difference between risedronate and 2-pyr EHDP lies in the location of the hydroxyl-ethane-bisphosphonate group:



P&G v. Teva (2009)

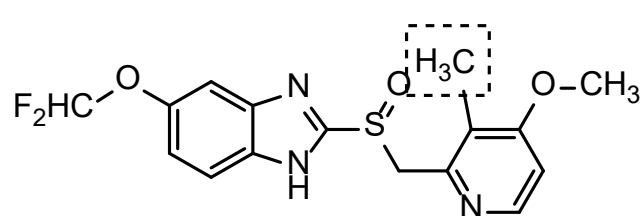
- Why is risedronate not obvious?
 - District court: Insufficient reason to select 2-pyr EHDP as lead compound
 - Fed. Cir.: “An obviousness argument based on structural similarity between claimed and prior art compounds ‘clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound.’” [citing to *Takeda* and *Eisai*]
 - “We need not reach this question because [it is not obvious] to modify 2-pyr EHDP to create risedronate.”
 - Evidence: Properties of bisphosphonates highly unpredictable
 - A leading authority in the bisphosphonate field stated in a prior art reference that “[t]o infer from one compound the effects in another is dangerous and can be misleading.”
 - No *prima facie* obviousness
 - “In this case, there is no credible evidence that the structural modification was routine.”
 - “Additionally, there was an insufficient showing that a person of ordinary skill in the art would have had a ‘reasonable expectation of success’ in synthesizing and testing risedronate.”
 - Even if *prima facie* obviousness, rebutted by unexpected results

P&G v. Teva (2009)

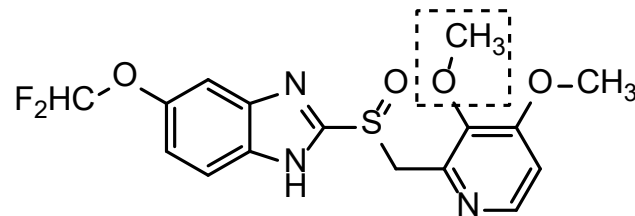
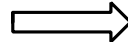
- PTO Guidelines:
 - Teaching point: “It is not necessary to select a single compound as a ‘lead compound’ in order to support an obviousness rejection. However, where there was reason to select and modify the lead compound to obtain the claimed compound, but no reasonable expectation of success, the claimed compound would not have been obvious.”
 - “Here, there was no evidence that the necessary modifications would have been routine, so there would have been no reasonable expectation of success.”
 - “It should be noted that the lead compound cases do not stand for the proposition that identification of a single lead compound is necessary in every obviousness rejection of a chemical compound. [Describes two examples] Thus, Office personnel should recognize that in certain situations, it may be proper to reject a claimed chemical compound as obvious even without identifying a single lead compound.”

Altana v. Teva (2009)

- The claimed compound pantoprazole, a proton pump inhibitor, the active ingredient in Altana's antiulcer drug Protonix[®], was obvious over the prior art Compound 12:
 - The only structural difference between Compound 12 and pantoprazole is the 3-position substituent on the pyridine ring.



Compound 12



Pantoprazole

Altana v. Teva (2009)

- Why is pantoprazole obvious?
 - “Thus, to establish a prima facie case of obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound in a particular manner.”
 - Ample evidence to select Compound 12 as a lead compound
 - Compound 12 was one of the more potent compounds in group of 18 disclosed compounds (and improvement over omeprazole)
 - Sufficient reason to modify the lead compound
 - Evidence that a 3-methoxy substituted pyridine ring would provide desired stability improvement compared to 3-methyl substituted analogue.
 - No requirement to identify a single lead compound
- Obviousness finding was preliminary (in context of denial of preliminary injunction).

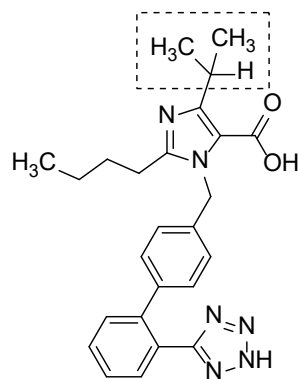
Altana v. Teva (2009)

- PTO Guidelines:
 - “Although the decision reached by the Federal Circuit in *Altana* involved a motion for a preliminary injunction and did not include a final determination of obviousness, the case is nevertheless instructive as to the issue of selecting a lead compound.”
 - Teaching point: “Obviousness of a chemical compound in view of its structural similarity to a prior art compound may be shown by identifying some line of reasoning that would have led one of ordinary skill in the art to select and modify a prior art lead compound in a particular way to produce the claimed compound. It is not necessary for the reasoning to be explicitly found in the prior art of record, nor is it necessary to the prior art to point to only a single lead compound.”

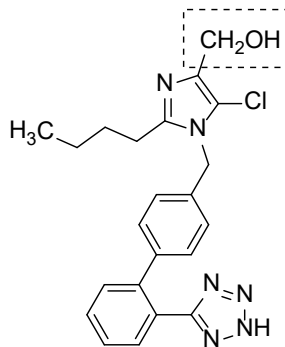
Daiichi v. Matrix (2010)

- The claimed compound olmesartan medoxomil, an angiotensin receptor blocker (“ARB”) for treating high blood pressure, the active ingredient in Daiichi’s Benicar[®], Benicar HCT[®], and Azor[®], was nonobvious over (1) the ‘902 patent ARB compounds, (2) the ‘069 patent Example 118, and (3) well known use of medoxomil as a prodrug, even though –
 - Example 6 of ‘902 patent differs from olmesartan by only a single oxygen atom
- “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.” [citing to *Dillon* and *Eisai*; also quoting *Dillon*]
- “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.” [citing *Eisai* and *Takeda*]

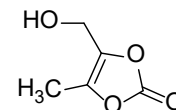
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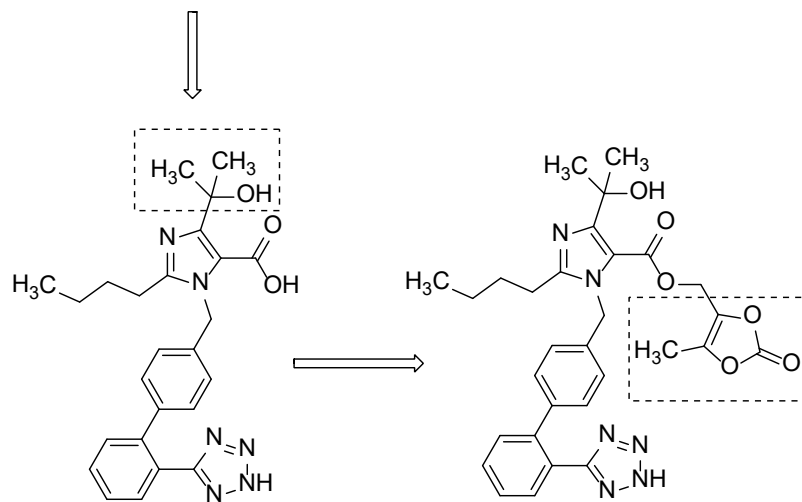
'902 Example 6



'069 Example 118



Medoxomil



Olmesartan

Olmesartan Medoxomil

Daiichi v. Matrix (2010)

- Why is olmesartan medoxomil not obvious?
 - No reason to select '902 ARBs as lead: many later ARBs more potent and better studied than the '902 ARBs
 - Even though '902 ARBs are structurally closest prior art
 - [Citing *Takeda* and *Eli Lilly*] “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. . . . 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. . . . Potent and promising activity in the prior art trumps mere structural relationships.”
 - No reason to modify
 - The prior art as a whole taught away from the use of a more hydrophilic substituent at the 4-position of the imidazole ring.
 - No reason to convert olmesartan into a disfavored medoxomil prodrug.

Scorecard

	Reason to Select	Reason to Modify/ Reasonable Expectation	Obvious
<i>In Re Dillon</i> (1990)			Yes
<i>Yamanouchi v. Danbury</i> (2000)	No	No	No
<i>Eli Lilly v. Zenith</i> (2006)	No	No	No
<i>Takeda v. Alphapharm</i> (2007)	No	No	No
<i>Eisai v. Dr. Reddy's Lab</i> (2008)	Yes	No	No
<i>P&G v. Teva</i> (2009)	--	No	No
<i>Altana v. Teva</i> (2009)	Yes	Yes	Yes*
<i>Daiichi v. Matrix</i> (2010)	No	No	No

*At Preliminary Injunction stage

BPAI Decisions

- *Ex Parte Cao* (Bd. Pat. App. & Int., Sept. 21, 2011) (non-precedential)
 - Issues:
 - “Must the rejection be reversed if it did not use a ‘lead compound’ analysis?”
 - “If a ‘lead compound’ analysis was required, does the fact that [the prior art compounds identified by the examiner] are less potent than others compel reversal?”
- Board’s decision and rationale
 - Obviousness rejection affirmed
 - Lead compound analysis not required
 - *Eisai* did not overrule *Dillon*: “presumed expectation that the structurally similar compounds have similar properties.”
 - Prior art compounds cited by examiner had similar structures and “effective” activity (even if orders of magnitude lower than other prior art compounds)
 - No evidence that claimed compounds had activity higher than cited compounds
 - Burden shifted to appellants to show unexpected results

BPAI Decisions

- *Ex Parte Subramanyam* (Bd. Pat. App. & Int., March 29, 2010) (non-precedential)
 - Issue
 - Structural similarity based on homology (length of alkyl chain)
 - Board's decision and rationale
 - Obviousness rejection reversed
 - Applies lead compound analysis (cites to *Dillon* and *Takeda*)
 - Rejection based solely on structural similarity
 - » No evidence or reasoning for selection of cited compound as lead
 - “Such structural similarity, alone, however, is insufficient to establish a prima facie case of obviousness, as there must be some reason that would have led the ordinary artisan to the compound required by the claims.”

Questions?

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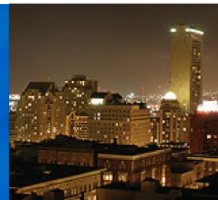
Orange County



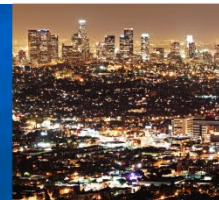
San Diego



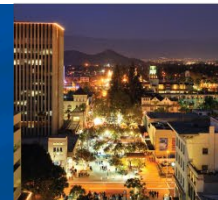
San Francisco



Silicon Valley



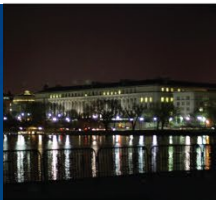
Los Angeles



Riverside



Seattle



Washington DC