When is Medicinal Chemistry Patently Obvious?

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In order to be granted a valid patent, an invention must be both novel and non-obvious (*i.e.* inventive) in light of what was public knowledge at the time. In a recent decision from the United States District Court of New Jersey[1] and later the US Court of Appeals for the Federal Circuit [2] (CAFC), the issue of whether it is obvious to modify a pharmaceutical compound by substituting a methoxy group for a methyl group has been considered.

Background

Altana Pharma holds, and exclusively licences to Wyeth, the patent for the compound pantoprazole, which is the active ingredient in Protonix®, a prodrug treatment for stomach ulcers. This compound is one of a family of compounds known as proton pump inhibitors (PPIs), one of the original and most famous of which is the blockbuster drug omeprazole (Fig. 1), the active ingredient in Losec® and Prilosec®.

In April 2004, Teva Pharmaceuticals and later in March 2005 Sun Pharmaceuticals (collectively "Teva") both filed applications to the FDA for approval to sell a generic version of Protonix®. Following these submissions, Altana Pharma and Wyeth (collectively "Altana") filed suit against Teva for patent infringement. In response, Teva conceded infringement of the Altana patent but argued that the patent was invalid because the invention was obvious in light of what was known at the time of filing. Altana then sought an interim injunction to prevent sales of the generic drugs while the case for patent invalidity makes its way through the courts.

This decision relates to the interim injunction, which means that at this stage it is not the validity of the patent *per se* which is at question. However, it can give an indication of strength of the case against the validity of a patent.

What was the basis of the argument that the invention was obvious?

To establish that an invention concerning the modification of a chemical compound is obvious in the United States it must be shown that, based on the knowledge publicly available at the time, a chemist would:

i. have some motivation for selecting a lead compound (the compound to be modified); and

ii. have some motivation for modifying the lead compound in the way that would produce the compound claimed as the invention.

With this in mind, Teva set out their argument for obviousness using four documents:

i. An earlier patent[3] owned by Altana that disclosed a number of compounds including a compound known as compound 12 as being potent PPIs (see Fig. 1).

ii. An article,[4] which Teva claimed taught that it would be desirable to lower the pKa of a PPI to 4, because it would improve the stability of the compound in the body.

iii. Another article[5] that Teva claimed taught that a methoxy group at the 3-position of a pyridine ring would provide a lower pKa than a methyl group in the same position.

iv. Finally, the patent for omeprazole[6], which Teva said demonstrated the feasibility of substituting a methoxy group for a methyl group at the 3-position of the pyridine ring in a PPI.

Teva argued compound 12 would be the lead compound and the other documents would give the means and motivation for modifying it to pantoprazole.

What is the other side of the argument?

Altana argued that there was no reason to select compound 12 over the approximately 90 compounds included in their own earlier patent (even though "compound 12" was included in an experimental section which demonstrated the activity of eighteen compounds). They also suggested that for a lead compound to be obvious, the prior art should point only to a single promising compound rather than the multitude of potential leads.

What was the outcome?

It would seem that the District Court was at least in part persuaded by the argument set out by Teva and refused to grant the interim injunction. Several factors are considered when deciding whether to grant an interim injunction. In this case, regarding the question of the validity of the patent, the District Court decided Teva had demonstrated a "substantial question of invalidity". The Appeals Court then found the District Court had not applied standards

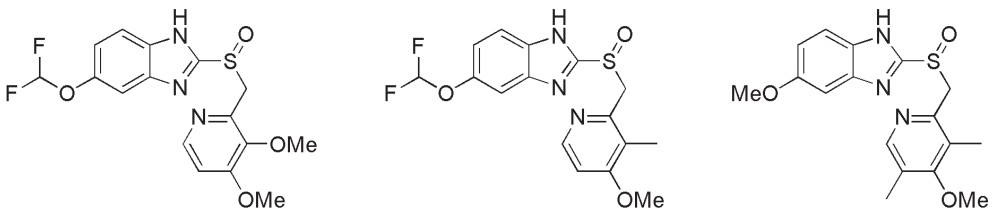

Fig. 1. The proton pump inhibitors (PPIs) at issue in the US Courts

which were clearly erroneous and therefore upheld the decision. However, there is a glimmer of hope for Altana, as one of the judges in the Appeals Court, while agreeing with the decision not to grant the interim injunction, stated that she did not believe the evidence established invalidity of the patent. Since this is only an interim injunction it is not necessary to establish invalidity, only a "substantial question of invalidity", therefore her comments were still in keeping with the judgement.

So it appears that Teva have won round one but, with the final decision on validity of the patent (and subsequent damages) still to come, this is a fight that has some time to run.

What does this mean for me?

Advances in medicinal chemistry are often made in increments, by making modifications to previously known pharmaceutical compounds or natural products. When engaging in this type of research (and hoping to patent the results) it is worth considering the two points set out above. Firstly, is the known pharmaceutical compound a natural choice as a lead compound? Remembering that when we say "natural choice" this should be based on public knowledge, not your own private research or gut instinct. Secondly, if it is a natural choice for further research, are the modifications based on standard chemistry with predictable beneficial results or are they based on trial and error or lead to surprising discoveries?

It is the element of unpredictability in medicinal chemistry which leads to patentable results.

For our next issue we ask you, the reader, to contact us with your burning questions regarding patents, patent ownership, or indeed any form of intellectual property:

Patent Proze

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References

1 *Altana Pharma AG v. Teva Pharma. USA, Inc*., Case No 04-2355, (D. N. J. Sept. 2, **2007**)

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