

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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*Ex parte* LILI ARABSHAHI and HAIJUAN LI

Appeal 2008-3325  
Application 10/200,096  
Technology Center 1600

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Decided: July 21, 2008

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Before, DEMETRA J. MILLS, LORA M. GREEN, and  
FRANCISCO C. PRATS, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness. We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

Claims 1, 11, 13, 21, and 23 are on appeal. Claims 1, 11 and 21 are representative of the appealed subject matter and read as follows:

1. A method of quantifying an HIV protease inhibitor in a biological sample, the HIV protease inhibitor selected from the group consisting of amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir, the method comprising:

combining HIV protease, a chromogenic peptide substrate for HIV protease, and the biological sample to form an assay mixture whereby an absorbance change is generated upon cleavage of the substrate by the protease;

monitoring the rate of substrate cleavage by measuring the absorbance change of the assay mixture; and

relating the rate of substrate cleavage to a concentration of the HIV protease inhibitor in the biological sample.

11. The method of claim 1, wherein the substrate comprises a polypeptide having an amino acid sequence consisting of the amino acid sequence of SEQ ID NO:3.

21. A test kit for quantifying an HIV protease inhibitor in a biological sample according to the method of claim 1, the kit comprising: a first container comprising HIV protease; and a second container comprising a chromogenic peptide substrate for the HIV protease wherein the protease inhibitor is selected from the group consisting of amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir and wherein the substrate comprises a polypeptide comprising a scissile bond between a first amino acid residue and a second amino acid residue wherein at least one of the first amino acid residue and the second amino acid residue is a p-nitrophenylalanine residue.

The Examiner relies on the following prior art references:

Zuk	US 4,281,061	Jul. 28, 1981
Sharma	US 5,171,662	Dec. 15, 1992

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Michael Barry et al., *Protease Inhibitors in Patients with HIV Disease: Clinically Important Pharmacokinetic Considerations*, 32 CLIN. PHARMACOKINET. 194-209 (1997)

Mihaly V. Toth and Garland R. Marshall, *A simple, continuous fluorometric assay for HIV protease* 36 INT. J. PEPTIDE PROTEIN RES. 544-550 (1990)

Peter J. Tummino et al., *Competitive Inhibition of HIV-1 Protease by Biphenyl Carboxylic Acids*, 316 ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS 523-528 (1995)

The rejections as presented by the Examiner are as follows:

1. Claims 1 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma in view of Toth and Barry.

2. Claims 1 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma in view of Toth, Barry and Zuk.

3. Claims 1, 11 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma in view of Toth, Barry and Tummino.

4. Claims 1, 21 and 23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma in view of Toth, Barry, Tummino and Zuk.

## DISCUSSION

### *Background*

“Currently, there are six HIV protease inhibitor compounds approved by the Food and Drug Administration (FDA) for treatment of AIDS patients - amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, and saquinavir.”

(Spec. 1).

The Specification discloses:

a method of quantifying an HIV protease inhibitor in a biological sample, comprising combining HIV protease, a

spectroscopic substrate for HIV protease, and a biological sample suspected of containing an HIV protease inhibitor to form an assay mixture; measuring a spectroscopic property of the assay mixture; and relating the spectroscopic property of the assay mixture to a concentration of the HIV protease inhibitor in the biological sample.

(Spec. 3.)

We select claims 1 and 21 as representative of the rejections before us since Appellants have not separately argued the other pending claims.

37 C.F.R. 41.37(c)(1)(vii).

1. Claims 1 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sharma in view of Toth and Barry.

The Examiner finds that

Sharma teaches detecting HIV protease activity by combining HIV protease with a substrate and a potential protease inhibitor test compound. ... The patent teaches that blood samples from an animal exposed to an inhibitor can be tested; "animal" is read to include humans because infected humans are exposed to protease inhibitors during the course of treatment. See column 7, lines 13-33. The principle element distinguishing Sharma from the claimed invention is that Sharma detects the cleavage fragments with specific antibodies rather than a chromogenic substrate, *per se*.

(Ans. 5.)

Thus the Examiner relies on Toth as teaching

an assay which combines HIV protease, p-nitrophenylalanine labeled substrate, and protease inhibitor. The cleavage products of the substrate are detected by fluorescence or UV absorption. See page 546. The reference goes on to

teach an acceptor chromophore on the last line of page 544. Toth teaches throughout the reference that a preferred label is p-nitrophenylalanine. This reference does not specifically teach applying the method to biological samples.

(Ans. 5.)

The Examiner concludes that:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Toth et al. to clinical samples to assess protease inhibitor concentrations in a patient's blood during the course of anti-HIV therapy. The Toth et al. method provides the advantage of a sensitive fluorescent assay without Sharma's additional antibody reagent for detecting substrate cleavage fragments. Thus, the instant invention is obvious over Sharma in view of Toth et al. because it would replace Sharma's antibody reagents with a sensitive, easy to detect label.

(Ans. 5-6.)

Barry is also relied on by the Examiner as disclosing "various routinely used protease inhibitors including those recited in claim 1."

(*Id.* at 6.) The Examiner further concludes that:

It would have been obvious to one of ordinary skill in the art at the time the invention was made to test clinical samples for routine therapeutic agents during the course of anti-HIV treatment. Because the prior art method teaches that protease inhibitors can be used, it would have been obvious to use the method with known proteases such as those disclosed by Barry for use in therapy. Thus, the instant invention is obvious over Sharma in view of both Toth et al. and Barry et al.

(*Id.* at 6)

Appellants, on the other hand, contend that the office has failed to establish a *prima facie* case of obviousness because, *inter alia*, the Office has failed to identify a legally sufficient suggestion or motivation to make presently claimed subject matter. . . [T]he applicants maintain that the motivation/suggestion proffered by the Office is too general, not specifically directed to the applicant's invention, and, therefore, legally insufficient.

(App. Br. 6.)

Appellants also argue that “[t]he prior art does not teach a chromogenic substrate. An antibody (as taught by Sharma) is not a chromogenic substrate. And the present specification makes clear that a chromogenic substrate as used in the present claims is distinct from a fluorescent substrate (as taught by Toth et al.)” (App. Br. 9).

We are not persuaded by Appellants’ arguments. To begin, the Examiner has articulated a motivation to combine the cited references. “In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. . . . [A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *KSR Int’l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741-42 (2007). Obviousness requires a teaching that all elements of the claimed invention are found in the prior art and “a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does” *Id.* at 1741. We find no error in the Examiner’s *prima facie* case of obviousness.

The Examiner has identified each of the claimed elements in the prior art and has identified a reason why a person of ordinary skill in the art would have been led to make the claimed subject matter. Furthermore, Sharma indicates that their method

contemplated equivalents thereof [which] include substrates and/or cleavage products which are detectable by means other than antibodies, for examples [sic] those which are detectable by their reaction with other components to form detectable products. One such embodiment would be a substrate that is an enzyme which functions in a biological reaction; the reaction being detectable. If cleaved by an HIV protease, the enzyme would be rendered non-functional. Alternatively, the enzyme can be a cleavage product which is only functional if the HIV protease cleaves the non-functioning substrate substrate. Essential elements of the present invention include a substrate which is converted by HIV protease cleavage into at least one cleavage product in which the substrate and/or at least one of the cleavage products are distinguishable.

(Sharma, col. 8, ll. 32-55.) Thus Sharma suggests that one of ordinary skill in the art consider methods such as that of Toth as equivalent to the use of antibody detection providing a clear motivation to combine the cited references.

Appellants argue that

Toth et al. teaches:

Our initial attempts focused on developing a chromogenic substrate. Because of the known accommodation of Phe Tyr at position P1 in HIV protease substrates, we prepared a series of potential substrate analogs containing p-NO<sub>2</sub>-Phe at either P1 or P1'. Of the compounds we examined which were octapeptides or smaller, only the P1' analogs were substrates and the changes in absorbance upon hydrolysis were insufficient for a sensitive, continuous assay. (Emphasis added.)

(App. Br. 10 (quoting Toth 544).)

Appellants assert further:

The uncertainty is further accentuated by the fact that Toth et al. does not even teach the method in a biological sample. For this reason as well, the presently claimed chromogenic assay cannot be obvious over Sharma in view of Toth et al. and Barry et al.

(*Id.*)

However, the claims are not limited to continuous assays. In addition, Sharma states that kinetic assays for HIV protease are known to include “HPLC assays, cleavage of a radiolabeled decapeptide, and spectrophotometric assays utilizing chromogenic and fluorogenic compounds.” (Sharma, col. 1, ll. 35-40.) Furthermore, the text following the above excerpt from Toth, at page 444, col. 2, indicates that Nashed and Tomazek “have reported a spectrophotometric assay based on cleavage of chromogenic substrates containing p-NO<sub>2</sub>-Phe at position P1.” “[W]hen the question is whether a patent claiming the combination of elements of prior art is obvious” the relevant question is “whether the improvement is more than the predictable use of prior art elements according to their established functions.” *KSR*, 127 S.Ct. at 1740. Therefore we find that the evidence supports that it is known in the art that chromogenic means can be used according to its established function, to detect HIV protease.

In view of the above, we find that a preponderance of the evidence supports a finding of obviousness of the claimed subject matter. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office).

2. Claims 1 and 21 are rejected under 35 U.S.C. § 103(a) as obvious over Sharma in view of both Toth et al. and Barry et al., further in view of Zuk et al.

The relevance of Sharma, Toth and Barry are discussed above. Zuk is relied on by the Examiner for teaching “that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (column 22, line 62, to column 23, line 4).” (Ans. 7).

The Examiner concludes that:

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the necessary reagents to perform the diagnostic assay in a kit format for the convenience and economy of the user. One would have been motivated to assemble the reagents in a kit format to standardize the reagents for the optimization of the assay for use in a clinical diagnostic laboratory or physician’s office. Thus, the instant invention is obvious over Sharma in view of both Toth et al. and Barry et al., further in view of Zuk et al.

(*Id.*)

Appellants contend that they “have detailed the deficiencies of the combination of Sharma, Toth et al., and Barry et al. above and submit that Zuk et al. fails to provide any teachings that compensate for these deficiencies.” (App. Br. 10). As discussed herein, we find no deficiencies in the disclosure of Sharma, Toth and Barry. Having no further argument from Appellants, the rejection is affirmed.

3. Claims 1, 11, and 13 are rejected under 35 U.S.C. § 103(a) as obvious over Sharma in view of Toth, Barry and Tummino.

The Examiner contends that

[t]he claimed invention is further limited to SEQ ID NO:3.

The relevance of Sharma, Toth et al., and Barry et al. has been set forth above.

Tummino et al. teaches SEQ ID NO: 3. See page 523. It would have been obvious to one of ordinary skill in the art to use Tummino's sequence as a matter of design choice from among known substrate sequences. The artisan would find this particular sequence especially desirable and would be motivated to use it because it is commercially available from Bachem Bioscience Inc. One using this sequence in a continuous assay would expect that it would be fully functional in allowing the monitoring of the rate of substrate cleavage and thus correlating the rate with the concentration of enzyme inhibitor in a biological sample. Therefore, the instant invention is obvious over Sharma in view of (Toth et al., Barry et al., and Tummino et al.).

(Ans. 8.)

Appellants contend that they have detailed the deficiencies of the combination of Sharma, Toth, and Barry and submit that Tummino fails to provide any teachings that compensate for these deficiencies. (App. Br. 11).

As discussed herein, we find no deficiencies in the disclosure of Sharma, Toth and Barry. Having no further argument from Appellants, the rejection is affirmed.

4. Claims 1, 21<sup>1</sup>, and 23 are rejected under 35 U.S.C. § 103(a) as obvious over Sharma in view of Toth et al., Barry et al., and Tummino et al., further in view of Zuk et al.

The relevance of Sharma, Toth et al., Barry et al., and Tummino has been set forth above. “Zuk et al. teach that reagents for an immunoassay can be provided as kits as a matter of convenience and to optimize the sensitivity of the assay in the range of interest (column 22, line 62, to column 23, line 4).” (Ans. 8).

The Examiner contends that:

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include the necessary reagents to perform the diagnostic assay in a kit format for the convenience and economy of the user. One would have been motivated to assemble the reagents in a kit format to standardize the reagents for the optimization of the assay for use in a clinical diagnostic laboratory or physician’s office.

(Ans. 9.)

Appellants contend that they have detailed the deficiencies of the combination of Sharma, Toth, Barry, Tummino and submit that Zuk fails to

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<sup>1</sup> Claim 21: Although not separately argued by Appellants we feel claim 21 requires specific comment. Claim 21 is directed to a kit comprising a protease inhibitor and a substrate which is p-nitrophenyl-alanine. Toth describes an assay using the claimed components. While appellants have argued that Toth uses fluorescence to detect the substrate instead of detecting absorbance of a chromogen, this argument is not relevant to the composition claim, as Toth describes each of the claimed components. We therefore affirm the rejection of claim 21 for obviousness.

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provide any teachings that compensate for these deficiencies. (App. Br. 11). As discussed herein, we find no deficiencies in the disclosure of Sharma, Toth and Barry. Having no further argument from Appellants, the rejection is affirmed.

#### SUMMARY

The obviousness rejections are affirmed.

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

AFFIRMED

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