

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 25

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte DONALD J. KYLE and
ROGER N. HINER

Appeal No. 1997-2518¹
Application 08/359,642²

HEARD: October 12, 2000

Before WILLIAM F. SMITH, SCHEINER and GRIMES , Administrative Patent Judges.
SCHEINER, Administrative Patent Judge.

¹ As a preliminary matter, we note that this appeal is related to appeals in Application Serial Nos. 08/167,051 and 08/302,988 (Appeal Nos. 1997-0100 and 1997-1309), also heard on October 12, 2000. We have considered the three appeals together.

² Application for patent filed December 20, 1994.

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DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 2, 4 and 5, all the claims remaining in the application.

The references relied on by the examiner are:

Patchett et al. (Patchett)	4,483,850	Nov. 20, 1984
Eur. Pat. App. (Henke)	0 370 453	May 30, 1990

Hock et al. (Hock), "Hoe 140 A New Potent and Long Acting Bradykinin-Antagonist: In Vitro Studies," Br. J. Pharmacol., Vol. 102, pp. 769-774 (1991).

A reference discussed by the merits panel is:

Stewart et al. (Stewart)	4,923,963	May 8, 1990
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Claims 1, 2, 4 and 5 stand rejected under 35 U.S.C. § 112, first paragraph, and also under 35 U.S.C. § 103. As evidence of obviousness, the examiner relies on Henke, Hock and Patchett. We reverse both rejections.

BACKGROUND

As explained in the specification, pages 2 through 4:

Bradykinin (BK) is a nonapeptide generated as a result of the activity of kallikreins, a group of proteolytic enzymes present in most tissues and body fluids, on kininogens.

Bradykinin, and its physiologically important related peptides . . . exhibit physiological actions which qualify them as mediators of inflammatory reactions, hypotensive states, and pain. Bradykinin is overproduced in pathological conditions such as septic shock, anaphylaxis, rhinitis, asthma . . .

In addition to its analgesic and proinflammatory effects, bradykinin is a vasodilator. Because of its ability to lower blood pressure, bradykinin has

been implicated in the pathogenesis of several shock syndromes . . .
Bradykinin is also a potent bronchoconstrictor . . .

Thus, a bradykinin inhibitor or bradykinin receptor antagonist is expected to possess a number of desirable biological effects in the treatment, for example, of inflammation, septic shock, asthma, burn pain, rhinitis and allergy.

According to appellants, the present invention is directed to bradykinin receptor antagonists “that act as specific and competitive inhibitors of the biological activities of bradykinin,” wherein the L-Pro at position seven of the native bradykinin is replaced by a D-hydroxyproline ether or a thioether derivative. In addition, the antagonists may include “modifications at other positions . . . which confer increased antagonist potency, resistance to enzymatic degradation, and/or tissue specificity.” Specification, page 1.

DISCUSSION

Enablement

Claims 1, 2, 4 and 5 stand rejected under the first paragraph of 35 U.S.C. § 112 as “[t]he specification is not enabling for the scope of e.g., claim 1.” Examiner’s Answer, page 3. The examiner’s conclusion is based on an analysis in keeping with that described in In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988):

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).

The examiner notes that claim 1 encompasses “a considerable number of possible substitutions or permutations” at positions other than seven, not exemplified in the specification. As “[t]he high unpredictability of the peptide art, particularly the Bk art, has been notoriously known,” and “no guidance or reasonable assurance is provided in the specification that would aid one . . . as to the specific combinations of residues that would produce the desired result,” “one skilled in the art would have to experiment unduly to achieve such result.” Examiner’s Answer, pages 3 through 5.

Having carefully considered the examiner’s commentary on pages 3 through 5 and 8 through 12 of the Examiner’s Answer and the arguments on pages 14 through 19 of appellants’ Brief, we hold that the examiner has not set forth a reasonable basis for questioning the enablement of the claims on appeal. In our view, there are two principal flaws in the examiner’s reasoning: equating a considerable quantity of experimentation with undue experimentation, and failing to acknowledge what was known in the art at the time of appellant’s invention.

The specification contains working examples demonstrating the synthesis and activity of several bradykinin antagonists within the scope of claim 1, specifically defines an additional hundred or so, and outlines methods for making, identifying and using others encompassed by the claim (pages 12 through 20, and Example 41). The crux of the invention, and a feature common to all of the antagonists, is the substitution of the L-pro at position seven of bradykinin with various D-hydroxyproline ethers or thioether derivatives.

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It is true that the specification demonstrates only a few antagonists with substitutions at positions other than seven. We accept, for the sake of argument, that synthesizing and testing a large number of compounds with the various substitutions claimed at positions in addition to seven would be time consuming and laborious. Nevertheless, as explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

In unpredictable art areas, this court has refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim. See, e.g., In re Goodman, 11 F.3d 1046, 1050-52, 29 USPQ2d 2010, 2013-15 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1212-14, 18 USPQ2d 1016, 1026-28 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991); In re Vaeck, 947 F.2d at 496, 20 USPQ 2d at 1445. Enablement is lacking in those cases, the court has explained, because the undescribed embodiments cannot be made based on the disclosure in the specification, without undue experimentation. But the question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation “must not be unduly extensive.” Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

Given the specification's straightforward protocols for synthesizing, identifying and using bradykinin antagonists with formulas corresponding to those of the claims, we are satisfied that the specification provides reasonable guidance for one skilled in the art to make and use bradykinin antagonists, in addition to those absolutely defined in the specification, and that the experimentation necessary, while considerable, would not be undue.

Moreover, there is evidence of record that, at the time of the invention, some guidance was available in the prior art. "[A] patent need not teach, and preferably omits, what is well known in the art." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). Stewart, a reference of record in this case,³ and discussed at length in related appeal nos. 1997-0100 and 1997-1309, discloses a series of bradykinin antagonists with substitutions at positions zero, two, three, five, six, seven and eight of the native bradykinin. According to Stewart, substitution at position seven is critical for antagonist activity, while the additional substitutions at positions zero, two, three, five, six and eight affect various properties of the antagonists. For example, substitutions at positions five, six and eight of an antagonist enhance potency, while substitutions at positions two and three confer tissue specificity. Tables I and II.

The examiner has not explained why the specification's straightforward protocols for synthesizing, identifying and using bradykinin antagonists, together with what was

³ Submitted with the Information Disclosure Statement filed March 7, 1995.

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known in the art at the time of the invention, does not satisfy the enablement requirement of 35 U.S.C. § 112.

Finally, to the extent that the examiner requires an assurance of certainty (“[t]here is insufficient bioassay data provided . . . which teaches that all of the possible Bk analogs would be effective as antagonist,” (Examiner’s Answer, page 3)) to demonstrate enablement, we note that no legal authority has been cited in support of this requirement. On the contrary, a requirement for certainty would be incompatible with any experimentation at all.

Accordingly, the rejection of claims 1, 2, 4 and 5 under 35 U.S.C. § 112, first paragraph is reversed.

Obviousness

Claims 1, 2, 4 and 5 stand rejected under 35 U.S.C. § 103, as unpatentable over Henke, Hock and Patchett.

Henke and Hock disclose bradykinin antagonists which “differ[] from the claimed peptide in that the claimed peptide has a hydroxyproline ether derivative at position seven [of native bradykinin] . . . as opposed to Henke’s or Hock’s D-Tic residue” (Examiner’s Answer, page 7).⁴

According to the examiner, Patchett “suggest[s] or teach[es] that the heterocycles hydroxyproline ether or thio ether derivative and Tic are known in the art to be equivalent,” and further, Henke suggests “the functional equivalence of said

⁴ Tic is the abbreviation for 1,2,3,4-tetrahydroisoquinoline-3-ylcarbonyl.

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heterocyclic compound, albeit at different position of the Bk sequence i.e. at position eight)” (Examiner’s Answer, pages 7 and 8).

It is well established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references. Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996) (citation omitted).

The examiner believes that “it would have been obvious . . . to replace the residue D-Tic residue at position seven of the Henke’s or Hock’s BK peptide sequence with a hydroxyproline ether or thio ether derivative since replacement of one heterocycle compound with another would expectedly result in a peptide having similar activity as taught by Patchett” (Examiner’s Answer, page 7). In our judgment, the examiner’s reason for modifying the prior art antagonists is without merit.

Patchett discloses a generic structural formula for peptide inhibitors of angiotensin converting enzyme (ACE). There are 26 alternatives suggested for the “heterocyclic elements” of the inhibitors, including hydroxyproline ethers and D-Tic. The examiner has not explained how interchangeability of these substituents in ACE inhibitors is at all relevant to the modification of bradykinin antagonists. There is no evidence of record that bradykinin and ACE (or their inhibitors/antagonists) are similar in structure or function; indeed, appellants maintain that ACE inhibitors and bradykinin antagonists are “different compounds with different pharmacological activities and

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therapeutic uses,” especially with respect to modulating blood pressure (Brief, page 25). Nor do we see anything in Patchett to indicate that the substituents listed are recognized as universal functional equivalents. Thus, we agree with appellant that even if Patchett “show[s] that substitution of oligopeptides with hydroxyproline material and Tic results in ACE inhibitory activity, the reference does not teach or suggest that the same substitution in bradykinin peptides would achieve bradykinin antagonist activity . . . even if the hydroxyproline material and Tic are functionally equivalent substituents in . . . ACE inhibitors, they would not necessarily be functionally equivalent substituents in [the claimed] bradykinin antagonists” (Brief, page 24).

We have no doubt that the prior art could be modified in a manner consistent with appellants’ specification and claims, but the fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested its desirability. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Here, we find no reason or suggestion stemming from the prior art which would have led a person having ordinary skill to the claimed method. In our opinion, the only reason or suggestion to combine the references in the manner proposed by the examiner comes from appellants’ specification. Accordingly, we find that the examiner’s initial burden of establishing a prima facie case of obviousness has not been met.

The rejection of claims 1, 2, 4 and 5 under 35 U.S.C. § 103 is reversed.

REVERSED

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