

THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 56

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SHIGEO MORIMOTO, TAKASHI ADACHI, TOHRU MATSUNAGA,
MASATO KASHIMURA, YOSHIAKI WATANABE and KAORU SOTA

Appeal No. 1996-1080
Application No. 07/869,111

ON BRIEF

Before KIMLIN, JOHN D. SMITH, and WALTZ, Administrative Patent Judges.

WALTZ, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the examiner's refusal to allow claims 1 through 3 as amended subsequent to the final rejection (see the amendment dated Aug. 12, 1994, Paper No. 48, entered as per the Advisory Action dated Sep. 2, 1994, Paper No. 49). Claims 1 through 3 are the only claims pending in this application.

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According to appellants, the invention is directed to a process for selectively methylating the 6-hydroxy position of erythromycin A, and intermediates useful in this process, which process does not involve the formation of quaternary salts at the 3'-dimethylamino position (Brief, pages 2-3). Claims 1 and 3 are illustrative of the subject matter on appeal and a copy of these claims is attached as an Appendix to this decision.

The examiner has relied upon the following references as evidence of obviousness:

| | | |
|---|-----------|----------|
| Faubl et al. (Faubl) | 4,640,910 | Feb. 3, |
| 1987 | | |
| Watanabe et al. (Watanabe) | 0 158 467 | Oct. 16, |
| 1985 | | |
| (Published European Patent Application) | | |

Kirk-Othmer, *Encyclopedia of Chemical Technology*, 3rd ed., Vol. 20, pp. 964-65, John Wiley & Sons, 1982.

Claims 1 and 2 stand rejected under 35 U.S.C. § 103 as unpatentable over Faubl in combination with Watanabe and Kirk-Othmer (Answer, page 2). Claim 3 stands rejected under 35 U.S.C. § 103 as unpatentable over Watanabe¹ in combination

¹The last digit is omitted from the citation of Watanabe on page 3 of the Answer. However, this is a harmless error since the entire prosecution of this application and parent application no. 07/094,888 recognize the correct citation of

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with Faubl and Kirk-Othmer (Answer, page 3). We *affirm* these rejections for reasons which follow.

OPINION

A. *Background*

According to appellants, this application is a continuation of application no. 07/094,888 (hereafter, the '888 application), now abandoned. The claims of the '888 application were finally rejected and this final rejection was appealed to the Board of Patent Appeals and Interferences (hereafter, the Board). A merits panel of the Board issued a decision dated Dec. 17, 1990, Paper No. 20, as a result of this appeal (Appeal No. 90-3119), affirming the examiner's rejections of claims 1 through 3 under 35 U.S.C. § 103 over Faubl and Watanabe, with the reference to Kirk-Othmer newly cited by the Board. This decision was later clarified in a Supplemental Decision dated Jan. 25, 1991, Paper No. 22, and modified after a Request for Reconsideration by reversing the examiner's rejection and denominating the rejections set forth in the original decision as new grounds of rejection under 37

this reference against claim 3 (also see the correct citation in the "Prior Art of record" on page 2 of the Answer).

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CFR § 1.196(b)(see the decision on Request for Reconsideration dated Apr. 12, 1991, Paper No. 24).

The claims as presented in Appeal No. 90-3119 differ in three aspects from the claims in this appeal. Claims 1 through 3 now on appeal are limited to a 6-O-methylerythromycin A derivative where both R² and R³ are trimethylsilyl instead of a "substituted silyl group" or hydrogen, "arylmethyl" is now benzyl, and "halogen" is now chlorine. Furthermore, appellants have submitted two Declarations by Watanabe under 37 CFR § 1.132 that were not of record in the prior appeal. Further background information is presented on pages 3-5 of the Brief. Accordingly, this merits panel of the Board must begin anew, evaluating all the arguments and evidence for and against patentability, uninfluenced by any earlier conclusion reached by an earlier Board upon a different record. *See In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).

B. The Rejection of Claim 3

Since the thrust of the invention is the process of preparation, we will first consider claim 3 on appeal. Claim

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3 stands rejected under § 103 over Watanabe in combination with Faubl and Kirk-Othmer (Answer, page 3).

The examiner finds, and appellants do not contest, that the process of Watanabe differs in only one aspect from the process recited in claim 3 on appeal, namely Watanabe teaches that the protecting groups for the hydroxy substituents of the erythromycin A derivative are esters while the process of claim 3 uses trimethylsilyl as a protecting group (Answer, page 4, and the Brief, pages 13 *et seq.*). Kirk-Othmer has been applied by the examiner for the disclosure that silylation is a conventional technique for protecting hydroxyl groups (Answer, page 3). The examiner also states that Faubl discloses that silylation is a conventional technique for protection of a hydroxy substituent in erythromycin derivatives (*Id.* at page 4). The examiner concludes that it would have been obvious to one of ordinary skill in the art to protect hydroxy substituents on the erythromycin derivatives of Watanabe by silylation instead of ester formation, as taught by Kirk-Othmer and Faubl (*Id.*).

We adopt the prior merits panel's finding that Kirk-Othmer discloses "silylation of hydroxyl groups as a known

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blocking or protective technique in organic syntheses generally and with regard to certain antibiotic compounds particularly." (Decision dated Dec. 17, 1990, Paper No. 20, page 2, see Kirk-Othmer, paragraph bridging pages 964-965). In view of this teaching and the uncontested findings regarding the method of Watanabe, we agree with the examiner's conclusion that silylation, instead of ester formation, to block or protect the hydroxyl groups of the erythromycin derivatives of Watanabe would have been well within the ordinary skill in the art.

For the foregoing reasons, we determine that the examiner has established a *prima facie* case of obviousness in view of the reference evidence. Appellants have submitted evidence of unexpected results in rebuttal to the examiner's evidence of obviousness. Accordingly, we must reevaluate the arguments and evidence for and against patentability based on the totality of the record. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Appellants have submitted and discussed three Declarations under 37 CFR § 1.132 by Watanabe (hereafter the Watanabe I, Watanabe II, and Watanabe III Declarations,

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executed on Apr. 19, 1990, June 6, 1991, and July 8, 1992, respectively)(see the Brief, pages 15-21). The Watanabe I Declaration and Experiments 7-10 of the Watanabe II and III Declarations are directed to a showing regarding the rejection of compound claims 1 and 2 on appeal, as discussed below. Furthermore, the Watanabe III Declaration is essentially the same as the Watanabe II Declaration (Brief, page 17, last paragraph). Therefore, with respect to the rejection of claim 3 on appeal, we will limit our discussion to the results of Experiments 1 through 6 of the Watanabe II Declaration.

Appellants admit that the reaction conditions in all of the Experiments were not the same (Brief, page 16).² Furthermore, at least one reaction variable differs between the process of Watanabe and the Experiments of the Watanabe II Declaration. After completion of the reaction, Watanabe adds triethylamine or sodium bicarbonate (see Example 40 or Example 42, referring to Example 16) while the Experiments of the Declaration use dimethylamine (see Experiment 1, page 2 of the Watanabe II Declaration). The cause and effect of the

²Contrary to appellants' admission on page 16 of the Brief, Experiments 3 and 5 were both reacted at different conditions (temperature and time) than Experiments 1, 2 and 4.

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different protecting groups is lost here since all the variables are not fixed. *In re Dunn*, 349 F.2d 433, 439, 146 USPQ 479, 483 (CCPA 1965). The declarant fails to set forth any reasoning for employing "larger scale" reactions than those disclosed by Watanabe, which, for some unexplained reason, produces far less yield than reported by Watanabe (see Experiments 1, 2 and page 15 of the Brief). As noted by the examiner on page 5 of the Answer, the claims are also not limited to any reaction conditions or specific methylating agents while the showing in the Declaration is limited to a particular methylating agent and specific reaction conditions. Therefore the Declaration evidence has not been shown to be reasonably predictive of or commensurate in scope with the claimed subject matter. *In re Boesch*, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980).

Finally, we note that it is not enough that the results for the claimed subject matter and the prior art invention are different, as shown in Table 1 on page 5 of the Watanabe II Declaration. Appellants must demonstrate that such results are unexpected. *In re Geisler*, 116 F.3d 1465, 1469-70, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997); *In re Merck & Co., Inc.*,

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800 F.2d 1091, 1099, 231 USPQ 375, 381 (Fed. Cir. 1986). The Declarant has not stated or demonstrated that the results summarized in Table 1 are unexpected (Watanabe II Declaration, page 8, paragraph (2)).

For the foregoing reasons, we determine that, based on the totality of the record, including the arguments and evidence presented for and against patentability, the preponderance of evidence weighs most heavily in favor of obviousness within the meaning of § 103. Accordingly, the rejection of claim 3 under § 103 as unpatentable over Watanabe in combination with Faubl and Kirk-Othmer is affirmed.

C. The Rejection of Claims 1 and 2

Claims 1 and 2 stand rejected under § 103 as unpatentable over Faubl in combination with Watanabe and Kirk-Othmer (Answer, page 2). Since appellants have stated that claims 1 and 2 stand or fall together (Brief, page 6), we decide this rejection on the basis of claim 1 alone (see 37 CFR § 1.192(c)(5)(1993)).

The examiner finds that Faubl discloses a "closely analogous erythromycin derivative" but fails to disclose the

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claimed R¹ substituents (i.e., the 9-oxime substituents, see the sentence bridging pages 2-3 of the Answer). The examiner applies Watanabe to show that the claimed substituents for the 9-oxime derivative are known in the art, again citing Kirk-Othmer for the teaching that silylation is conventional for protecting hydroxy substituents (Answer, page 3).

Appellants argue that only by extensive picking and choosing of substituents from the generic formula of Faubl could one of ordinary skill in the art arrive at compounds analogous to the claimed compounds (Brief, paragraph bridging pages 6-7). Furthermore, appellants do not contest the equivalency of oxime substituents taught by Watanabe but argue that this reference cannot be combined with Faubl since its teaching is in "an entirely different context," i.e., directed to a process for 6-methylation (Brief, page 7).

Faubl discloses a generic formula (II) where there are several selections of variables (column 2, lines 15-39). However, the choices for each variable are relatively few, with "preferred" compounds directing one of ordinary skill in the art to various "trimethylsilyl", 4''-hydroxy (i.e., B is OH), and R₆= methyl derivatives (column 2, lines 39-48). The

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examples also suggest or direct the artisan to various silylated and 9-oxime derivatives (see examples 3, 4 and 11). Watanabe teaches various substituents at the 9-oxime position that result in protection of that position during methylation (see page 3). Accordingly, we agree with the examiner's position that substitution of the alkenyl and benzyl substituents taught by Watanabe for the alkyl group exemplified at the 9-position by Faubl would have been well within the skill in the art.³ Both Faubl and Watanabe are directed to antibiotics and methods of protecting various substituents of erythromycin derivatives.

For the foregoing reasons, we determine that the examiner has established a *prima facie* case of obviousness in view of the reference evidence. As previously noted, appellants have submitted three Declarations by Watanabe to rebut the examiner's evidence of obviousness. The Watanabe I Declaration and Experiments 7 through 10 of the Watanabe II Declaration have been submitted by appellants to rebut the

³Conversely, the silyl derivatives of the substituted 9-oximes of Watanabe would have been well within the ordinary skill in the art given the teaching in Kirk-Othmer of conventional silylation of hydroxy substituents in antibiotics.

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rejection of claim 1 on appeal (Brief, pages 8-12).

Appellants submit that the Declaration evidence establishes, at the minimum, that it is difficult to deoximate the compounds of Faubl where the oxime is methyl, isopropyl or butyl substituted, when using sodium hydrogen sulfite as the deoximating agent (Brief, page 11, see the specification, sentence bridging pages 11-12).

The Watanabe I Declaration, in Experiments 4 and 6, and the Watanabe II Declaration, in Experiments 9 and 10, attempt to show that deoximation of alkyl-substituted 9-oxime erythromycin derivatives by the "ordinary method" of using sodium hydrogen sulfite is "difficult" (see pages 8-9, paragraph (3), of the Watanabe II Declaration). In every Experiment of these Declarations, some of the starting substituted oxime is converted to an unnamed product (e.g., see Experiment 4 of the Watanabe I Declaration, where 400 mg of starting material is reacted with only 320 mg of the starting material recovered after reaction). However, no evidence has been presented on this record regarding the ease or difficulty in deoximating the claimed alkenyl-substituted oximes. Therefore, on this record, there is no basis for

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comparison of the alkyl and alkenyl substituents at the 9-oxime position of the erythromycin derivatives. Declarant has not stated that the results of the deoxygenation experiments are unexpected. *In re Geisler, supra.*

For the foregoing reasons, we determine that the preponderance of evidence, based on the totality of the record including evidence and arguments for and against patentability, weighs in favor of obviousness within the meaning of § 103. Accordingly, the rejection of claims 1 and 2 under 35 U.S.C.

§ 103 over Faubl in combination with Watanabe and Kirk-Othmer is affirmed.

D. Summary

The rejection of claim 3 under 35 U.S.C. § 103 as unpatentable over Watanabe in combination with Faubl and Kirk-Othmer is affirmed. The rejection of claims 1 and 2 under 35 U.S.C. § 103 as unpatentable over Faubl in combination with Watanabe and Kirk-Othmer is affirmed.

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

AFFIRMED

| | | |
|-----------------------------|---|-----------------|
| EDWARD C. KIMLIN |) | |
| Administrative Patent Judge |) | |
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| |) | BOARD OF PATENT |
| JOHN D. SMITH |) | APPEALS |
| Administrative Patent Judge |) | AND |
| |) | INTERFERENCES |
| |) | |
| |) | |
| |) | |
| THOMAS A. WALTZ |) | |
| Administrative Patent Judge |) | |

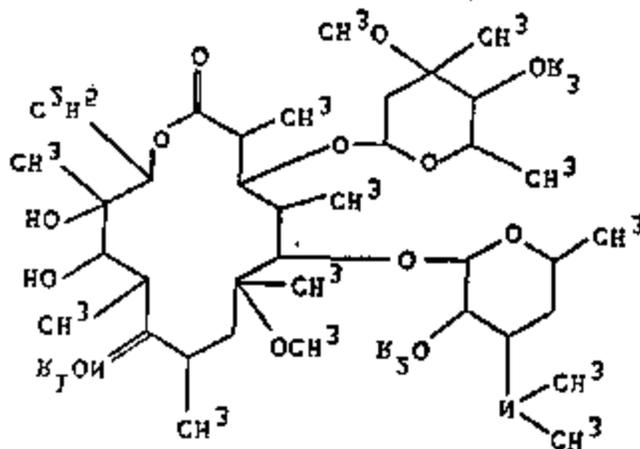
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APPENDIX

Κ₂ και Κ₃ της φημερλγαιγγλγ
εγκοχλστρουλγ δλοηδ μβαλνδ ζ το ε στρου ερωηδ' αυδ
εγκοχλ δλοηδ μβαλνδ γ το ε στρου ερωηδ' ε ηρτο δλοηδ οκ αυ
ε ρουαλγ δλοηδ απρατρεπεδ ρλ γ το ζ ολ ε στροιηε ερωηδ' αυ
ε ρουαλγ δλοηδ' οκ
ε ζ-εγκουλγ δλοηδ μβαλνδ ζ το γδ στρου ερωηδ'
μρελετη Κ₂ γε:



εοικηηε:

γ ε-ο-μερλγελετρλοηλστυ γ οελτβετλε κερκεεουρεδ ρλ ερε

լեւեալագոյն ընդ ընդ լոկալիտ:

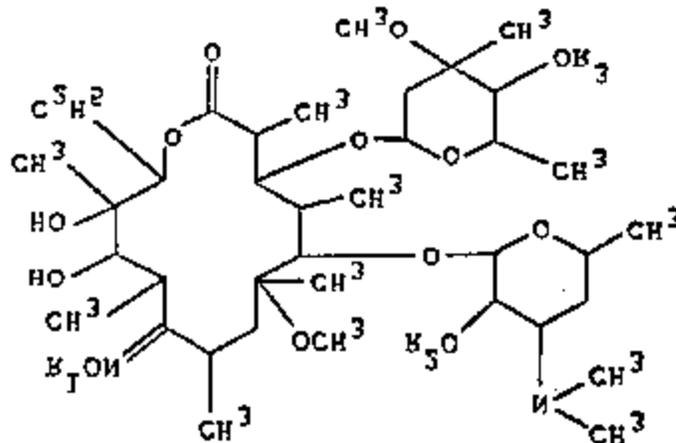
սրբազանագոյն սրբազանագոյն սրբազանագոյն K_2 ձեւով լո ձեւով և լոկալիտ
 K_2 լո ձեւով լոկալիտ սրբազանագոյն K_2 լո ձեւով լոկալիտ սրբազանագոյն
և լոկալիտ սրբազանագոյն K_2 -X (լոկալիտ
լոկալիտ սրբազանագոյն լոկալիտ լոկալիտ սրբազանագոյն

K_2 և K_2 ձեւով լոկալիտ լոկալիտ

սրբազանագոյն ձեւով լոկալիտ K_2 լո ձեւով լոկալիտ սրբազանագոյն և
սրբազանագոյն ձեւով լոկալիտ K_2 լո ձեւով լոկալիտ սրբազանագոյն և
և լոկալիտ ձեւով սրբազանագոյն լոկալիտ K_2 լո ձեւով լոկալիտ սրբազանագոյն և
և լոկալիտ ձեւով և

և K_2 -սրբազանագոյն ձեւով լոկալիտ K_2 լո ձեւով լոկալիտ սրբազանագոյն

լոկալիտ K_2 լո:



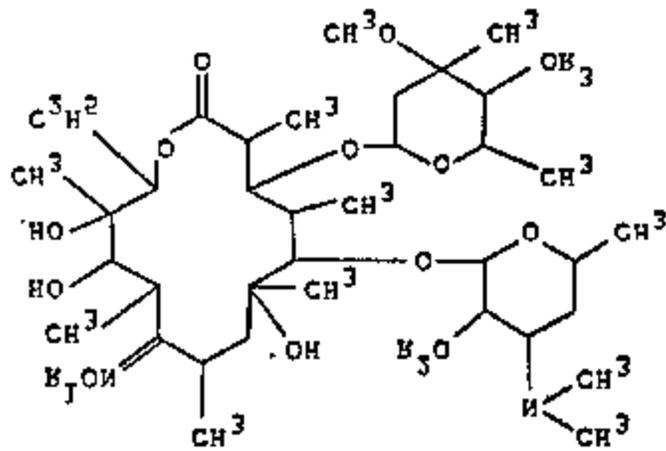
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լեւեալագոյն ընդ ընդ լոկալիտ:

3. և լոկալիտ լոկալիտ սրբազանագոյն և լոկալիտ սրբազանագոյն և լոկալիտ սրբազանագոյն

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αὐτῆς συνβολῆς οἱ ἑσκαπῆς II εἶναι ἡ μεθυλινοῦ ἑδεῖς·
(ἡμετεῖν B₁, B₂ καὶ B₃ εἶναι ὡς ἀποφῆσθαι ἐπὶ τῶν ἀποφῆσθαι)



II

Leticia

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APJ WALTZ

APJ KIMLIN

APJ JOHN D. SMITH

DECISION: AFFIRMED
Send Reference(s): Yes No
or Translation (s)
Panel Change: Yes No
Index Sheet-2901 Rejection(s):

Prepared: March 18, 2002

Draft Final

3 MEM. CONF. Y N

OB/HD GAU

PALM / ACTS 2 / BOOK
DISK (FOIA) / REPORT