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D E C I S I O N
of 8 October 2004

Case Number: T 0773/02 - 3.3.1

Application Number: 96945192.1

Publication Number: 0820449

IPC: C07D 305/14

Language of the proceedings: EN

Title of invention:
Paclitaxel analogs, preparation and use as antitumor agents

Applicant:
Xechem, Inc.

Opponent:
-

Headword:
Paclitaxel analogs/XECHEM

Relevant legal provisions:
EPC Art. 54, 111(1), 123(2)

Keyword:
"Main request: novelty (yes) - diastereoisomers not disclosed unambiguously by a prior art describing the racemate"
"Remittal to the first instance for further prosecution"

Decisions cited:
T 0296/87

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0773/02 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 8 October 2004

Appellant: Xechem, Inc.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 19 October 2001 refusing European application No. 96945192.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

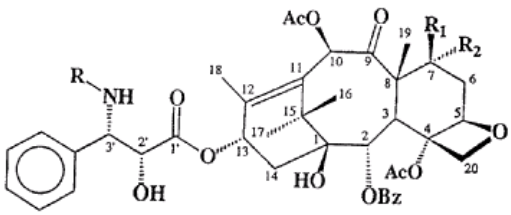
Chairman: A. J. Nuss
Members: P. F. Ranguis
J. H. Van Moer

Summary of Facts and Submissions

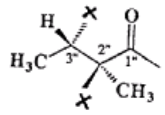
I. This appeal lies from the decision of the Examining Division to refuse the European application No. 96 945 192.1 on the ground that the subject-matter of Claim 1 of the set of claims received on 21 August 1997 was anticipated by the disclosure of document (1) US-A-5 470 866 pursuant to Article 54(2) EPC.

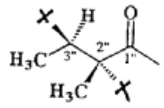
II. The refused set of claims contained thirty one claims. Claim 1 read as follows:

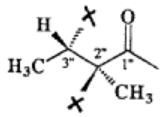
"1. A compound of the formula:

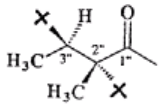


wherein R is selected from:

R =  $R_1 = OH$ $R_2 = H$;

R =  $R_1 = OH$ $R_2 = H$;

R =  $R_1 = H$ $R_2 = OH$; and

R =  $R_1 = H$ $R_2 = OH$;

and X is halogen."

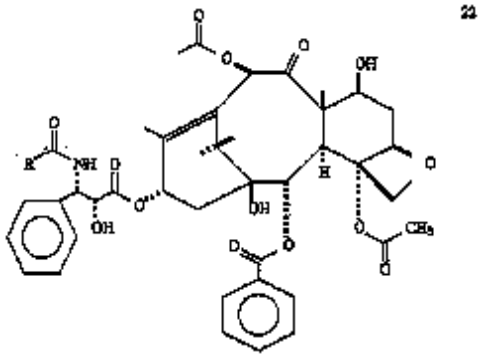
Claim 9 had the same wording as Claim 1 with the further limitation that X was bromine.

Claim 20 had the same wording as Claim 1 with the further limitation that X was chlorine.

III. The Examining Division held in its decision that the disclosure of document (1) specifically described a 2", 3" side-chain halogenated N-debenzoyl-N-acyltaxol derivative comprising the $CH_3CHBrCBr(CH_3)CO$ acyl group (cf. Table 4 and compound of general formula **30**) and was considered for this reason as novelty destroying with regard to the subject-matter of Claim 1.

IV. In the statement of grounds of appeal, the Appellant disputed that document (1) disclosed either explicitly or implicitly the claimed compounds since the skilled man in reading the disclosure of the compound at Table 4 and the method of preparation thereof described at columns 21 and 22 would have no way of knowing exactly what the structure of the compound tested was. Furthermore, Claim 1 was directed to stereospecific compounds, whereas document (1) merely disclosed a list of compounds in racemate form. Decision T 296/87 was cited in that respect.

V. In a communication, the Board pointed out that document (1) disclosed the N-acyl taxol of formula **22** (column 21, lines 1 to 18)



and that the N-acyl groups recited on Table 4, identified unambiguously N-acyl taxols of formula 22, where R was $CH_3CHBrCBr(CH_3)$-. Furthermore, a process for preparing such a compound was disclosed (cf. column 5, lines 13 to 23. column 18, line 38 to column 20, line 67).

VI. In response, the Appellant pointed out that the method of preparation which the Board referred to was described in general terms and gave no guidance to retain the stereocentres in the correct configurations. In particular, the success of the final step referring to a transfer of the acyl group from O to N depended upon the nature of the acyl group undergoing transfer. Acyl groups containing stereocentres were prone to configurations changes/racemization during such transfer reactions. Furthermore, the reference made in Table 4 to $CH_3CHBrCBr(CH_3)$- related to the racemate and not the diastereoisomers defined in Claim 1.

VII. The Appellant requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC - Amendments*

2.1 The claims directed to a method for treating animal or human tumors were reworded as a compound for use in a method for treating animal or human tumors (cf. Claims 3, 11, 12, 22 and 23), which change was necessary under EPC (Article 52(4) EPC). Apart from that, the subject-matter of Claims 1 to 11 corresponds to the subject-matter of Claims 1 to 11 as originally filed. The subject-matter of Claim 12 corresponds to the subject-matter of Claims 12 to 15 as originally filed. The subject-matter of Claim 13 corresponds to the subject-matter of Claim 16 as originally filed. The subject-matter of Claims 14 to 22 corresponds to the subject-matter of Claims 17 to 25 as originally filed. The subject-matter of Claim 23 corresponds to the subject-matter of Claims 26 to 29 as originally filed. The subject-matter of Claim 24 corresponds to the subject-matter of Claim 30 as originally filed. The subject-matter of Claims 25 to 31 corresponds to the subject-matter of Claims 31 to 37 as originally filed.

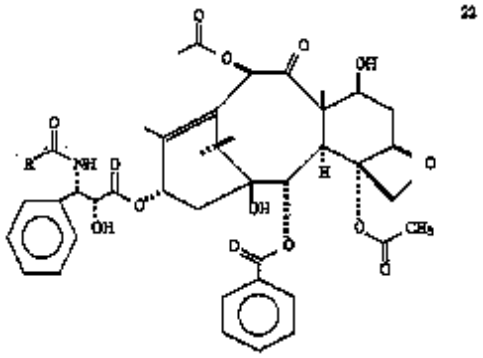
2.2 The Board is satisfied that the amendments comply with the requirements of Article 123(2) EPC. No objection was raised by the Examining Division either.

3. *Article 54 EPC - Novelty*

3.1 The subject-matter of Claim 1 relates to (2"R, 3"S)-dihalocephalomannine, (2"R, 3"S)-dihalo-7-epi-

cephalomanninne, (2"S, 3"R)-dihalocephalomannine and (2"S, 3"R)-dihalo-7-epi-cephalomanninne (cf. point II above).

3.2 Document (1), the sole prior art cited in the examination proceedings discloses a process for converting taxol or cephalomanninne to N-acyl analogs of taxol (cf. column 18, lines 38 to 40). Treatment of taxol with a desired acylating reagents converts it to a 2'-acyltaxol derivative **18**. Protection of **18** at the C-7 position with 2,2,2-trichloroethylchloroformate yields the protective derivative **19**. Treatment of **19** with oxalyl chloride followed by water yields the oxamic derivative **20**. Treatment of **20** with diphenylcarbodiimide yields the N-acyl derivative **21** by deoxalylation followed by O-acyl -> N-acyl to yield the N-acyl taxol **22**.



(cf. column 5, lines 13 to 23 and column 18, line 38 to column 21, line 17).

Among the N-acyl group of the N-debenzoyl-N-acyltaxols cited in Table 4 (cf. column 29, lines 12 to 30), the $CH_3CHBrCBr(CH_3)CO$- group is explicitly mentioned.

For the skilled reader, there is a direct and unambiguous correspondence between the N-acyl taxol **22** and the acyl group $CH_3CHBrCBr(CH_3)CO$- cited in Table 4,

so that the N-acyl taxol **22** wherein R is $CH_3CHBrCBr(CH_3)$- is identified along with the process for its preparation in following the instructions set out above, individualizing, therefore, the 2",3"-dibromocephalomannine.

The Appellant argued that the description was not enabling in that the success of the final step referring to a transfer of the acyl group from O-acyl to N-acyl depended upon the nature of the acyl group undergoing transfer. However, this allegation that the person skilled in the art could not carry out the disclosed process is not supported by facts that can be checked and is, therefore, unsubstantiated.

3.3 The Board concurs however with the Appellant that the reference made in document (1), Table 4, to $CH_3CHBrCBr(CH_3)$- relates to a racemate. This document does not mention the four possible diastereoisomers for the group $CH_3CHBrCBr(CH_3)$-, nor does it describe how to obtain the individual stereospecific compounds (2"R,3"S)-dibromocephalomannine, (2"R,3"S)-dibromo-7-epicephalomanninne, (2"S,3"R)-dibromocephalomannine and (2"S,3"R)-dibromo-7-epi-cephalomanninne encompassed by Claim 1. That document does not, therefore, point unambiguously to those configurations even though those configurations were conceivable (cf. T 296/87, OJ EPO 1990, 195, points 6.2 and 7.1 of the reasons).

3.4 The Board concludes that document (1) is concerned only with racemates which do not affect the novelty of the (2"R,3"S) and (2"S,3"R) forms defined in the subject-matter of Claim 1. That finding applies *mutatis*

mutandis to the subject-matter of the Claims 9 wherein X is bromine.

The subject-matter of Claim 20 is also novel since document (1) does not disclose a 2", 3"-dichlorocephalomannine.

4. *Remittal to the first instance - Article 111(1) EPC*

4.1 The Board has come to the conclusion that the subject-matter of Claim 1 of the main and sole request met the requirement of Article 54 EPC overcoming, therefore, the sole reason supporting the refusal of the European application by the first instance. As stated above, that finding also applies to Claims 9 and 20.

4.2 Having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance, the Board exercises its discretion under Article 111(1) EPC to remit the case to the first instance for further prosecution.

4.3 When examining further the compliance of the Claims with EPC, the Examining Division should pay particular attention to the following:

The scope of Claims 4 to 8 seems to encompass a method for the preparation of the **racemate** form of 2", 3"-dihalocephalomannine or 2", 3"-7-epicephalomannine.

Claim 13 does not seem to include the separation of the diastereoisomers (cf. page 24 of the description). The

same remark would seem to apply to Claim 24 (cf. point 6.6, pages 56 to 57 of the description).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

N. Maslin A. Nuss