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D E C I S I O N
of 7 August 2001

Case Number: T 0288/98 - 3.3.1

Application Number: 91301891.7

Publication Number: 0448254

IPC: C07D 311/58

Language of the proceedings: EN

Title of invention:
Process and intermediates for 2R-benzyl-chroman-6-carbaldehyde

Patentee:
PFIZER INC.

Opponent:
Merck Patent GmbH

Headword:
Chroman esters/PFIZER

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious to try with a reasonable expectation of success"

Decisions cited:
T 0536/88, T 0694/92, T 0296/93

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0288/98 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 7 August 2001

Appellant: (Opponent)
Merck Patent GmbH
Postfach
Frankfurter Strasse 250
D-64293 Darmstadt (DE)

Representative:
-

Respondent: (Proprietor of the patent)
PFIZER INC.
235 East 42nd Street
New York, N.Y 10017 (US)

Representative:
Ruddock, Keith Stephen
Pfizer Limited
European Patent Department
Ramsgate Road
Sandwich
Kent CT13 9NJ (GB)

Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 23 January 1998 concerning maintenance of European patent No. 0 448 254 in amended form.

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
S. C. Perryman

Summary of Facts and Submissions

I. Notice of opposition was filed on the grounds of Article 100(a) EPC that Claims 1 to 5 for ES and Claims 4 to 8 for AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL and SE of European patent No. 0 448 254 did not meet the requirements of novelty and inventive step. The opposition was supported *inter alia* by documents

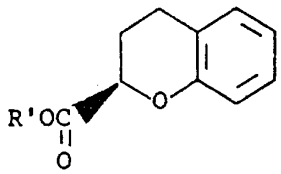
(1) EP-A-0 325 954 and

(2) J. Org. Chem. 55(3), pages 812 to 815, 1990.

The appeal lies from the Opposition Division's interlocutory decision, dispatched on 23 January 1998, that Claims 1 to 5 for ES and Claims 4 to 8 for AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL and SE, received on 20 May 1996, were found to meet the requirements of novelty and inventive step.

Claim 4 for AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL and SE, which was identical with Claim 1 for ES, read:

"A process for the preparation of an optically active (C_1-C_3)alkyl 2R-chroman-2-carboxylate of the formula



(II)

which comprises the steps of:

(a) partially hydrolysing the corresponding racemic (C_1-C_3)alkyl chroman-2-carboxylate in a reaction-inert solvent comprising water in the presence of a catalytic amount of a microbial lipase (derived from Pseudomonas fluorescens) to form a mixture comprising said (C_1-C_3)alkyl 2R-chroman-2-carboxylate and 2S-chroman-2-carboxylic acid; and

(b) recovering said (C_1-C_3)alkyl 2R-chroman-2-carboxylate from said mixture."

Claims 5 to 8 for AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL and SE and Claims 2 to 4 for ES were dependent upon Claim 4 respectively Claim 1.

II. The Opposition Division was of the opinion that it could not be predicted that lipase derived from *Pseudomonas fluorescens* would effect the same enantioselective hydrolysis on unsubstituted chroman-2-carboxylic acid esters as on chroman-2-carboxylic acid esters having a hydroxy substituent at position 6 or 7, as described in document (1).

III. Oral proceedings before the Board of appeal took place on 7 August 2001.

IV. The Appellant (Opponent) recognised the novelty of the claimed process but contested that it met the requirements of inventive step. In particular, he submitted that it was known from document (2) that a broad spectrum of substrates may be used in the enantioselective hydrolysis using lipase derived from *Pseudomonas fluorescens* and that chromans were known to be suitable substrates. Consequently, a skilled person could expect with a reasonable expectation of success

that the same enantioselective hydrolysis would occur with hydroxy substituted chroman-2-carboxylic acid esters as with such esters not bearing a hydroxy group.

V. The Respondent essentially argued that it follows from documents (1) and (2) that small changes in the chemical structure of the substrate may have dramatic influences on the enantioselective hydrolysis of lipase derived from *Pseudomonas fluorescens*. Therefore, in the absence of any specific teaching in the prior art, it is not possible to predict the result of using a particular enzyme on a particular substrate.

VI. The Appellant requested that the decision under appeal be set aside and that European patent No. 0 448 254 be revoked.

The Respondent requested that the appeal be dismissed and that the patent be maintained.

Reasons for the Decision

1. The appeal is admissible.

2. *Claim 4 for AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL and SE and Claim 1 for ES*

2.1 The Board has reached the conclusion that those claims meet the requirements of Article 123(2) and (3) EPC and that they are novel over the cited prior art. Since this was not disputed any more, it is not necessary to give detailed reasons for this findings.

Therefore, the only point at issue in the present case

is whether the claimed process meets the requirement of inventive step.

2.2 Both Parties were of the opinion that document (1) represented the closest state of the art.

In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is necessary to establish the closest state of the art being the starting point, to determine in the light thereof the technical problem which the invention addresses and solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

The "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

According to the patent in suit the optically active (C_1-C_3) alkyl 2R-chroman-2-carboxylates obtained from the claimed process are suitable intermediates in the preparation of a particular known hypoglycemic agent (see page 4, lines 44 to 46), whereas document (1) concerns a method of preparing optically pure enantiomeric chroman-2-carboxylic acids esters being substituted in their 6- or 7-position by a hydroxy group, which are suitable intermediates in the preparation of certain antiallergic and antiinflammatory compounds (see page 5, lines 23 to 30).

Chromans in order to be suitable as intermediates in

the preparation of the antiallergic and antiinflammatory compounds must carry a hydroxyl group in the phenyl moiety of the chromane structure, whereas chromanes suitable as intermediates in the hypoglycemic agent must be unsubstituted in the phenyl moiety. Consequently, the hydroxy substituted chromanes known from document (1) cannot be considered to be concerned with subject-matter aiming at the same objective as the unsubstituted chromanes obtained according to the claimed process.

Therefore, document (1) cannot be considered to represent a suitable starting point in assessing inventive step.

Since the only available prior art mentioning optically active chroman-2-carboxylic acids and corresponding alkyl esters is the reference in the introductory part of the patent in suit (see page 2, lines 20 to 23) to Schaaf et al., J. Med. Chem., volume 26, pages 328 to 334 (1983), this document, further referred to as document (6), is considered to represent the only suitable starting point in assessing inventive step.

Document (6) is mentioned in the description of the patent in suit on page 2, lines 18 and 19, as it was in the application as filed. The mentioned prior art was not submitted before the Opposition Division or during appeal proceedings and thus it might be a question whether or not this prior art can be considered by the Board in these proceedings. In the present case, the Board is of the opinion that for the examination of an inventive step it is necessary to objectively examine the complete prior art on file for equally objectively finding out the problem which was to be solved by the

claimed subject-matter. The Board follows with this view the decision T 536/88 (OJ EPO, 1992, 638) stating that while documents cited and discussed in the patent in suit are in principle not automatically subject-matter of an opposition appeal proceedings, this does not extend to a prior art document in a European patent which is discussed as essential prior art in relation to which the technical problem to be solved is formulated. Such a prior art document forms part of the documents to be discussed in an opposition appeal proceedings, even if it was not expressly mentioned within the time limit for the opposition. Document (6) is such a document, and so can be considered.

2.3 Document (6) describes in the left-hand column on page 334 under the headings "15-(l-2,3-Dihydro-2-benzopyranyl)-ù-pentanorprostaglandins $F_{2á}$ and E_2" and "15-(d-2,3-Dihydro-2-benzopyranyl)-ù-pentanorprostaglandins $F_{2á}$ and E_2" a method of preparing the enantiomers of unsubstituted chroman-2-carboxylic acid and the methylesters thereof by adding l-amphetamine to a solution of racemic chroman-2-carboxylic acid and collecting the resultant salt by filtration, thus separating one enantiomeric chroman-2-carboxylic acid in crystallised form from the other enantiomeric form solubilised in the mother liquid, and subsequently esterifying each enantiomeric chroman-2-carboxylic acid with methanol.

2.4 In view of the teaching of document (6), the technical problem underlying the patent in suit consists in the provision of a **further** process of preparing unsubstituted 2R-chroman-2-carboxylates in a simple way and in high yield (see the patent in suit, page 2,

line 44).

The patent in suit claims to solve this problem with the claimed process (see point I above).

2.5 The first point to be considered in assessing inventive step is then whether it has been convincingly shown that by the process according to Claim 1 the problem underlying the patent in suit has effectively been solved.

It has never been contested that by the data presented in Example 2 of the patent in suit a credible case has been put forward that the problem underlying the invention, as defined in point 2.4 above, is effectively solved by the claimed process.

2.6 Therefore, it remains to be decided whether a skilled person would have expected that by the claimed process (C_1-C_3)alkyl 2R-chroman-2-carboxylates of formula (II) could be prepared in a simple way and in high yield.

2.7 It was not contested that when trying to solve the above stated problem, the man skilled in the art is aware that document (1) describes in examples 1 and 2 the separation of the enantiomeric forms from racemic ethyl chroman-2-carboxylate having a hydroxy group in its 7-position by partially hydrolysing the racemic mixture in an aqueous reaction-inert solvent in the presence of a catalytic amount of lipase enzyme derived from Pseudomonas fluorescens, wherein the S-enantiomer is selectively hydrolysed and subsequently separating the S-enantiomer in its carboxylic acid form from the R-enantiomer as ethyl ester by generally known extraction methods and that document (2), which

concerns the enantioselective hydrolyses of a variety of 2-substituted racemic esters catalysed by lipase derived from *Pseudomonas fluorescens*, teaches that *Pseudomonas fluorescens* has shown specificity for the S-enantiomer of all 2-substituted esters tested and that it has a broad spectrum of substrate specificity. In particular, it describes the enantioselective hydrolysis of a number of 2-substituted hexanoic acid esters and it says that the broad spectrum of substrates includes chromans such as the 3,4-dihydro-7-hydroxybenzo[b]pyran-2-carboxylic acid ethyl ester (see page 812, left hand column, second paragraph, and Table I).

2.8 The Respondent contested however that it could be deduced from any of documents (1) and (2) that the same enantioselective hydrolysis would occur by using a lipase derived from *Pseudomonas fluorescens* in the hydrolysis of unsubstituted chroman-2-carboxylate esters as in the hydrolysis of chroman-2-carboxylate esters having a hydroxy group in its 7-position.

As support of this argument, the Respondent referred to page 4, lines 14 to 31 and 45 to 48 of document (1), saying that it was known that relatively minor changes in the substrates may have a serious impact on the enantioselectivity of the hydrolysis of alkyl esters and that kinetic resolutions catalysed by lipase have the disadvantage that the specificity of the enzyme often cannot be predicted for a given substrate. Furthermore, the Respondent referred to Table 1 of document (2), from which it follows that enantioselective hydrolysis of 2-substituted hexanoates occurs only for fluoro, hydroxy and bromo 2-substituents, whereas no reaction is observed for

trifluoromethyl and ethyl 2-substituents.

2.9 However, the passages referred to in document (1), apart from relating to some state of the art acknowledged in that patent application, concern the specificity of certain microorganisms or certain enzymes and do not give any information about the enantioselectivity of lipase derived from *Pseudomonas fluorescens*. It is only by the disclosure of the process for preparing optically pure enantiomers of chroman-2-carboxylate esters bearing an hydroxy group in its 6- or 7-position, as exemplified by the enantioselective hydrolysis of racemic ethyl 7-hydroxy-chroman-2-carboxylate in example 2, that any information is given about the enantioselectivity of lipase derived from *Pseudomonas fluorescens*.

Additionally, the information obtainable from Table 1 of document (2) may not be taken in isolation, but should be considered in combination with the complete teaching of this document. In the discussion given on page 814 (see the paragraph bridging the left-hand column and the right-hand column) it is namely said that lipase derived from *Pseudomonas fluorescens* has displayed excellent stereoselectivity in the hydrolysis of 2-substituted racemic esters and that the substituents at the C-2 position accepted by the enzyme have been fluorine, chlorine, bromine, hydroxy, as evidenced by the data in Table 1, and cyclic ethers, under which case chromans fall. The teaching of document (2) is thus not restricted to the enantioselective hydrolysis of 7-hydroxy-chroman-2-carboxylate esters, but it concerns the enantioselective hydrolysis of 2-substituted racemic esters in general and chroman-2-carboxylate esters in

particular. Moreover, it gives at least a general indication that lipase derived from *Pseudomonas fluorescens* may enable an enantioselective hydrolysis of chroman-esters.

2.10 The correct approach in assessing inventive step is not whether a skilled person would derive from given information in the prior art a sure predictability of success, as submitted by the Respondent, but rather whether it would be obvious to try something with a reasonable expectation of success, which implies the ability of a skilled person to reasonably predict, on the basis of the existing knowledge, a successful conclusion of an experiment (see point 28.5 in the Reasons for the Decision of T 694/92, OJ EPO 1997, 408, and point 7.4.4 in the Reasons for the Decision of T 296/93 of 28 July 1994).

2.11 In the present case, neither document (1) nor document (2) provides a skilled reader with such information that unsubstituted chroman-2-carboxylate esters can confidently be regarded as suitable substrates, but rather these documents provide a strong indication that with these success is plausible. Consequently, a skilled person would have tried the hydrolysis of racemic chroman-2-carboxylate esters with lipase derived from *Pseudomonas fluorescens* with a reasonable expectation of success that the esters would be hydrolysed in an enantioselective way.

2.12 Since in document (1) the alcohol part of the chroman ester may be alkyl, aryl or aralkyl, that are defined widely, whereas the chroman is defined narrowly, namely as 6- or 7-hydroxy, the Respondent argued that the teaching of document (1) was undoubtedly that a 6- or

7-hydroxy group is essential for the reaction to proceed.

As document (1) is concerned with a method of preparing intermediates which must bear an hydroxy group in the aromatic part in view of its presence required in the desired end product, the presence of the 6- or 7-hydroxy functionality is indeed essential there. From that, however, it cannot be concluded that the presence of an hydroxy-group is essential for the reaction to proceed. Moreover, since the carboxylate function is subsequently converted to another functionality in order to prepare the antiallergic and antiinflammatory compounds referred to in document (1), page 5, lines 23 to 30, the nature of the alcohol part of the ester cannot be regarded as critical.

2.13 The Respondent also alleged that the 2-substituent in 6- or 7-hydroxy-chroman-2-carboxylates is different from the one in unsubstituted chroman-2-carboxylates. Since it follows from Table I of document (2) that small changes in structure may not be tolerated in the enantioselective hydrolysis with lipase derived from *Pseudomonas fluorescens*, he submitted that a skilled person could not have expected with a reasonable expectation of success that such enantioselective hydrolysis would also occur in unsubstituted chroman-2-carboxylate esters.

In the absence of any support for that allegation, however, the Board does not see that a skilled person would have been prevented by such different substitution quite far away from the 2-C atom from trying to also carry out the hydrolysis with lipase obtained from *Pseudomonas fluorescens*.

2.14 For certainty as to whether a lipase obtained from *Pseudomonas fluorescens* would be effective to resolve the chroman now claimed, an experiment admittedly would be necessary. But such an experiment would be a routine matter, and not involve anything like the research with uncertain outcome that would have been necessary in cases considered by the Boards of Appeal where reasonable expectation of success has been denied. As acknowledged even by the Respondent's expert at the oral proceedings, based on prior art document (6) it was definitely worth running the experiment. There have been no indications here that the conditions suggested in document (6) would not serve to resolve the chroman whose resolution is now claimed, so the Board must presume that the skilled person would find that the method of document (6) works for this chroman. Checking up, by performing a relatively simple experiment, whether or not the most promising line suggested by the prior art solves a problem or not, is something that the skilled person can be presumed to carry out as a matter of routine. The absence of certainty cannot in such circumstances mean that there was no reasonable expectation of success.

2.15 Consequently, the Board comes to the conclusion that the claimed process does not involve an inventive step in the sense of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin A. Nuss