BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Publication in the Official Journal ~~Yes~~ / No

File Number: 116/90 - 3.3.1

Application No.: 80 301 052.9

Publication No.: 0 018 135

Title of invention: Xanthine derivatives, a process for their preparation and their use in pharmaceutical compositions

Classification: C07D 473/06

D E C I S I O N
of 18 December 1991

Proprietor of the patent: BEECHAM - WUELFING GMBH & CO KG

Opponent: HOECHST AKTIENGESELLSCHAFT, FRANKFURT

Headword: Xanthine ketals/BEECHAM-WUELFING

EPC Articles 54, 56, 114(1), (2)

Keyword: "novelty of a group of compounds represented by a generic formula (yes); applying T 12/90 dated 23 August 1991" - "disregarding a late filed submission by the Opposition Division (discretion rightly applied)" - "inventive step (confirmed)" - "structurally closely related compounds - non-obvious alternative to known pharmacologically active compounds".

Headnote

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 116/90 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 18 December 1991

Appellant : (Opponent)
HOECHST AKTIENGESELLSCHAFT, FRANKFURT
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Representative :

Respondent : (Proprietor of the patent)
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Decision under appeal :
Interlocutory decision of Opposition Division of the European Patent Office dated 7.12.89 maintaining the European patent No. 0 018 135 in amended form pursuant to Article 102(3) EPC.

Composition of the Board :

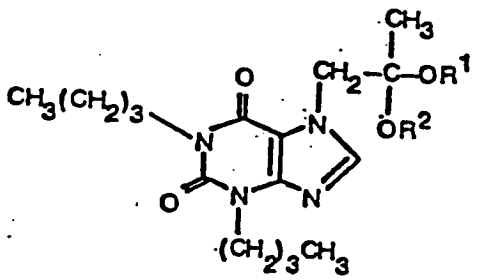
Chairman : K. Jahn
Members : P. Krasa
J.C. Saisset

Summary of Facts and Submissions

I. The mention of the grant of patent No. 0 018 135 in respect of European patent application No. 80 301 052.9 filed on 2 April 1980, was published on 28 September 1983 (cf. Bulletin 83/39) on the basis of eight claims.

Claims 1, 2, 5 and 8 read as follows:

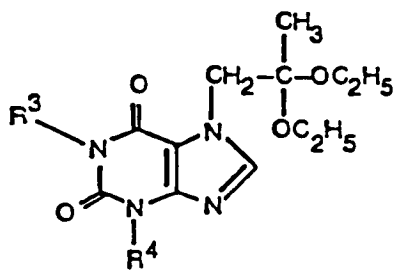
"1. A compound of the formula (II)



(II)

wherein
R^1 is a C_1-$_4$alkyl group and R^2 is a C_1-$_4$alkyl group; or R^1 is linked to R^2 so that OR^1 and OR^2 moieties and the carbon atom to which they are attached form a 1,3-dioxacyclohexa-2,2-diyl, 1,3-dioxacyclopenta-2,2-diyl or 1,3-dioxacycloheptа-2,2-diyl diradical.

2. A compound of the formula (III)

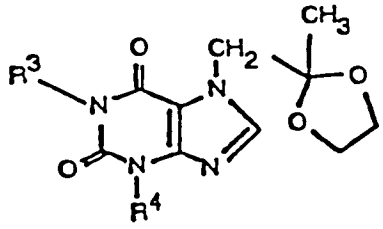


(III)

wherein

R^3 and R^4 are the same or different C_2-$_4$alkyl.

5. A compound of the formula (IV)



(IV)

characterised in that R^3 and R^4 are as defined in Claim 2.

8. A compound according to any one of Claims 1 to 5 for use in the treatment of peripheral vascular disease."

II. A notice of opposition was filed on 27 June 1984 requesting revocation of the patent on the ground of lack of inventive step.

The opposition was based on

(1) GB-A- 759 981.

In the course of the Opposition proceedings additional documents were cited, inter alia,

(1a) AT-A-186 250,
(2) GB-A-1 441 562,
(2a) DE-A-2 402 908,
(5) DE-B-1 212 542,
(8) FR-M-7 390.

The Appellant especially relied also on comparative tests which were filed by the Respondent in the German Patent

Office on 14 March 1979 in the course of the examination proceedings relating to document (2a), which corresponds to citation (2).

III. On 10 June 1987 the Opposition Division posted to the parties a communication in which, referring to the oral proceedings of 17 February 1987, the Respondent (Patentee) was requested to provide technical evidence, not merely written arguments "...in order to substantiate the presence of inventive step...".

The Respondent, on 10 October 1987, submitted pharmacological data for two ketals of the patent in suit and for two ketals of ketones which were disclosed in (2). Furthermore, he filed a number of scientific documents relating to the use of vasodilators in the treatment of peripheral vascular disease (= pvd).

The Opposition Division, in a communication according to Rule 58(4) EPC posted on 27 April 1988, informed the parties that they intended to maintain the patent in amended form and invited the parties to file their observations within a period of one month. The Appellant (Opponent) objected to this intention on 3 June 1988 and filed supplementing statements on 12 July 1988.

The Respondent, on 23 September 1988, requested the Appellant's second, supplementing submission be disregarded by the Opposition Division in view of its late filing. This request was contested by the Appellant as there were no provision in Rule 58 EPC which hinder a party from filing supplementing observations independent of any time limits.

IV. In a decision, dated 7 December 1988, the Opposition Division maintained the patent in amended form. The claims

of the amended patent differed from those as granted only by the amendment of a clerical error in Claim 7.

The Opposition Division held that document (2) was the closest prior art. This document disclosed a group of ketones encompassing the parent ketones of the presently claimed ketals having the same pharmacological properties as these ketals. The technical problem, in view of this prior art, was to find additional compounds useful in the treatment of pvd. It was decided that the solution of this problem, i.e. the provision of the compounds of Claims 1, 2 and 5, was not obvious as the ketals did not merely act as pro-drugs of the corresponding ketones, but had an activity per se which was demonstrated by their intraduodenal administration.

In respect to the Appellant's submission of 12 July 1988, the Opposition Division took the position, that this was to be disregarded for the sake of expeditious proceedings. The decision further stated: "Moreover it appears that the present late submissions are not relevant to such an extent so that the Opposition Division would be forced to change its mind in a radical manner." (See paragraph 3, last sentence of the impugned decision).

V. An appeal was filed against this decision on 14 February 1990 with payment of the prescribed fee. A Statement of Grounds of Appeal was filed on 14 March 1990. On 23 May 1990, the Opposition Division issued a further decision in which it corrected an error in its previous decision under Rule 89 EPC, the error being that the previous decision had not stated that it was an interlocutory decision within Article 106(3) EPC.

Then, following the issue of this decision under Rule 89 EPC, the Appellant filed a further notice of appeal on

2 June 1990, paid a further appeal fee and requested that the previously filed grounds of appeal should apply to the later filed appeal; furthermore, he requested the refund of one appeal fee.

Responding to a communication on behalf of the Board expressing the intention to refund the appeal fee and to proceed as if the second appeal had not been filed, the Appellant did not object to this view.

In an interlocutory decision of 3 December 1990, this Board decided that the appeal fee paid by the Appellant on 2 June 1990 should be refunded.

VI. In his written submissions and during oral proceedings held on 18 December 1991, the Appellant (Opponent) argued that the Respondent's comparative experiments were not carried out with prior art compounds, i.e. the ketones of (2), but rather with ketals which were not state of the art and that these comparative tests were not, therefore, suitable to support inventive step for the subject-matter of the disputed patent.

He further submitted that an invention could not be found in a minor structural change of a known chemical compound, if the new compound resulting therefrom had about the same effect as the known one. The chemist would expect that only minor changes in the properties are linked to such a minor structural change.

When looking for possible structural changes to known compounds, the normal organic chemist would consider modifications of functional groups first. Starting from the ketones known from (2), it would have been obvious for him to prepare the ketals as the ketones could be

regenerated therefrom and ketal formation from ketones is a simple reaction, familiar to every chemist.

Furthermore, (5) and (8) demonstrate that acetals, which were allegedly structurally closely related to ketals, and ketals have the same pharmacological properties as the respective parent compounds. Moreover, ketals of xanthine derivatives were mentioned in (1). Although they were disclosed there as intermediates, this was, in the Appellant's opinion, nevertheless, a pointer to the presently claimed compounds.

In respect to the pharmacological properties of the compounds disclosed in (2), the parties agreed that its contractility increasing effect in ischaemic skeleton muscles was already state of the art in view of a test report filed in the German Patent Office on 14 March 1979 in the course of the examination procedure of (2a) which corresponds to document (2).

The Appellant also criticised the Opposition Division for disregarding his submission of 12 July 1988.

VII. The Respondent did not reply to the grounds of appeal. As previously indicated, he also did not attend oral proceedings.

The Appellant requested that the decision under appeal be set aside and that the patent in suit be revoked.

At the end of the oral proceedings the Chairman announced the decision of the Board to dismiss the appeal.

Reasons for the Decision

1. The appeal is admissible.

2. Procedural issues

The Board concurs with the Appellant's submission that it would not have been correct for the Opposition Division to disregard a submission, which, as at the present case, was received in the EPO about one and a half years prior to rendering the decision, without paying any attention to its relevance. This results from the EPO's obligation under Article 114(1) EPC to examine the facts of its own motion. This obligation takes precedence over considerations regarding an economical and expeditious procedure.

However, in the impugned decision, the Opposition Division stated that they did consider the Appellant's submission of 12 July 1988 (see paragraph IV), but that it was not found to be so relevant as to require them to change their opinion on the case. Only then did the Opposition Division decide, exercising its discretion under Article 114(2) EPC, to disregard this submission.

The Board has checked whether there was a misuse of the discretion by the Opposition Division and concludes that there was none.

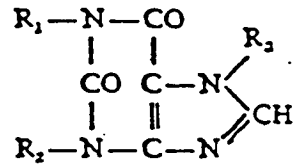
3. Amendments

The present claims are, apart from the amendment of an obvious error in Claim 7, those claims as granted which in turn are properly supported by the application documents as originally filed (see pages 2 to 4 and the examples). Thus, they comply with the requirements of Article 123 EPC.

4. Novelty

After examination of the cited documents, the Board has concluded that the claimed subject-matter is novel. While novelty was not in dispute in the appeal proceeding and, thus, a thorough discussion of this matter would not be mandatory, the Board deems it appropriate to deal briefly with document (1a) in this connection.

This citation discloses compounds of the generic formula



wherein R_1 and R_2 are alkyl groups with up to 5 C-atoms each, and R_3 is an allyl group, an acetonyl group or a group convertible into an acetonyl group, especially a propargyl group (page 1, lines 1 to 9).

The paragraph on page 1, lines 24 to 28, has also a bearing on the present issue. It reads (in English translation): "Suitable starting materials are, on the one hand, theophylline and, on the other hand, allyl bromide, propargyl bromide or chloroacetone. As halopropane derivatives e.g. ketals of chloroacetone may be used."

Thus, in the Board's judgement, document (1a) discloses in a generic manner also ketals of the 7-(2-oxopropyl)-xanthine derivatives of the above formula. No particular ketal is mentioned in (1a) or would be obtained necessarily in (the course of) the processes of the four examples given in (1a).

The compounds of present Claim 1 differ from those of document (1a) firstly in the requirement that both radicals R_1 and R_2 are identical, secondly that they are n-butyl, and thirdly by specifying the ketal group. This combination of selection of distinct structural features is a novel technical teaching which contributes a "new element" to the state of the art as required in the decision of this Board T 12/90 for establishing novelty (see T 12/90, paragraph 2.6, summarised in the supplement to issue 6/1991 of OJ EPO).

The compounds of present Claims 2 and 5 differ from those of document (1a) in defining the ketal group as the diethyl ketal or as the 1,2-ethylene ketal group, respectively. Again, this selection of a specific structural feature adds a new element to the state of the art which was not made available to the public by the latter.

For theses reasons the subject-matter of Claims 1, 2, and 5 is novel over citation (1a).

5. Problem and Solution

5.1 The patent in suit relates to a group of particular xanthine derivatives with good blood flow enhancing properties (page 2, lines 15 to 18) which may be used to treat vascular disorders such as intermittent claudication (page 3, lines 29 to 30; Claim 8).

Document (2), which the Board regards as the closest state of the art, relates to a group of particular 1,3 dialkyl-7-oxoalkylxanthines with a marked blood flow increasing effect in skeletal muscle (page 2, lines 21 to 23). The carbonyl group of the 7-oxoalkyl substituent is linked to

the xanthine residue via a group A, which is a "hydrocarbon radical having up to 4 carbon atoms which may be substituted by a methyl group" (page 1, lines 17 to 23). The most active compound was said to be 7-(3-oxobutyl)-1,3-di-n-butylxanthine (page 2, lines 23 to 24), where the carbonyl group is linked to the xanthine residue via an ethylene bridge. Its activity in ischaemic skeleton muscles was also known (see paragraph VI, above).

5.2 In the light of this closest prior art, the Board sees the technical problem underlying the disputed patent in finding additional compounds which may be used in the treatment of pvd.

According to the disputed patent this problem is solved by the compounds of Claims 1, 2, and 5.

In view of the experimental evidence available from the patent in suit (see pages 6 and 7) and from the Respondent's submission dated 10 October 1987, i.e. the increase of pO_2 and of contractility in skeletal muscles of cats under ischaemic conditions on intraduodenal administration of the claimed ketals, the Board is satisfied that the above technical problem has been credibly solved by the claimed compounds.

6. Inventive Step

It remains to be decided whether the claimed compounds meet the requirement of inventive step.

6.1 There is no indication in (2) how to obtain further peripheral vasodilators by modifying the xanthines disclosed there, let alone that the keto group should be functionalized to that end. The Appellant submitted that from documents (5) and (8) the skilled person would have

deduced that ketals would have the same or similar pharmacological properties as the parent ketones known from (2).

Document (5) discloses that the diethyl acetals of 3 theophyllino-propanal and of 3-theobromino-propanal are in the same way blood pressure lowering and coronary dilating as the natural purine compounds (page 1, left hand column, lines 38 to 45) and, furthermore, compares these diethyl acetals with the respective hydroxyethyl derivatives. Ketones of xanthine derivatives are not mentioned in (5). Thus, apart from the different pharmacological properties involved, the structural differences of the respective compounds are such that, in the Board's judgement and contrary to the Appellant's assumption, this citation would not allow any meaningful conclusions regarding the influence of the replacement of a keto group by a ketal group on the pharmacological properties.

Furthermore, the Appellant conceded in the oral proceedings that coronary dilation, peripheral vasodilation, and curing of pvd are distinct, separate pharmacological activities. Therefore, because a particular xanthine derivative possesses one of these activities, it is not possible to predict that it would also have either one or both of the other activities. By the same token, the Board is not convinced that reliable predictions are possible as regards the influence of the substitution pattern of the xanthines on their pharmacological profile.

Document (8) is concerned with substituted piperidine derivatives which comprise either a keto group or a 1,3-dioxolan-2,2-diyl group in a side chain attached to the piperidine ring. These piperidine derivatives have

tranquilizing and hypotensive activities (see page 1, left hand column and right hand column, lines 1 to 5). In view of these differences regarding the chemical structure and the properties of the compounds concerned, also this citation cannot serve as a pointer as to how to successfully solve the above technical problem.

6.2 The Board is not aware of any common general knowledge, according to which the skilled person could have assumed that the ketals of the xanthine ketones of (2) would also be useful in the treatment of pvd. The Appellant confirmed in the oral proceedings that he was not aware of any other document which could support the existence such common general knowledge.

6.3 Furthermore, the Appellant argued that the ketals are only pro-drugs of the ketones as they would be hydrolysed to give the corresponding ketone under the acidic conditions in the stomach. This allegation was refuted by the Respondent as not being supported by experimental evidence. In reply the Appellant relied on experiments which show that a ketal of pentoxiphylline decomposes within 20 minutes in artificial gastric juice. Pentoxiphylline, which is a 1-(5-oxohexyl)-xanthine derivative, was said to be entirely of the same nature as the compounds of the patent in suit. However, no evidence was given to support this statement. Under these circumstances not much weight can be attached to these experiments.

However, even if the Board were to accept that the claimed compounds, if orally administered as such, would be hydrolysed within a certain period of time due to instability with respect to the acidic gastric juice, this would not rule out the possibility that sufficient amounts of the ketals would pass through the stomach to exert a

pharmacological effect of their own, especially when administered in gastric-juice-resistant preparations.

6.4 The Respondent has demonstrated by introduodenally administering the claimed ketals that the compounds per se have a vasodilator activity (see paragraph 5.2, above).

The Appellant submitted in the oral proceedings that the ketals, after resorption from the duodenum, might undergo transformation and that, therefore, even on intraduodenal administration of the claimed compounds the parent ketones could be the active entity at the receptor site. In the absence of any experimental evidence in support, this allegation is disregarded by the Board (see also T 219/83 reported in OJ EPO 1986, 211).

6.5 The Appellant also submitted that a normal organic chemist faced with the above problem, would automatically modify the functional group, i.e. the carbonyl group of the compounds known from (2), and that ketal formation would be one of the simplest modifications which would occur to him. Hence, the claimed compounds had to be considered, in his opinion, as obvious with respect to citation (2). The Board doubts the existence of such a general principle that would induce the skilled person to always modify in the first instance functional groups of known pharmacologically active compounds when searching for alterna-tives; the preparation of e.g. homologes or isomers seems to be equally plausible for such purpose.

However, there is no need to further investigate this issue. There is no doubt that ketals are structurally closely related to the parent ketones and that, normally, there are no great difficulties to overcome in their preparation. Thus, the skilled person could have considered them as possible and perhaps easily obtainable

derivatives of the said parent ketones. This, however, is not the proper question to be asked. According to the established jurisprudence of the Boards it has to be investigated, when it comes to the issue of inventive step, whether a skilled person would have prepared the compounds in question with a reasonable expectation that they would successfully solve the technical problem under consideration. In the absence of any useful information to that end (cf. the above paragraphs 6.1 and 6.2) the Board cannot see why the skilled person would have suggested the claimed ketals with the expectation that they would be useful in the treatment of pvd.

6.6 In this connection the Board also notes that document (1a), already published in 1956 and mentioning as intermediates ketals of xanthine derivatives (cf. paragraph 4, above), evidently did not provide any incentive to the authors of document (2) with a priority of 1976. This indicates that experts ignored the ketals as possible pharmacological alternatives to the parent ketones in the field of peripheral vasodilating xanthines.

6.7 It follows therefrom that the subject-matter of Claims 1, 2, and 5 involves an inventive step. Dependent Claims 3 and 4, which relate to preferred embodiments of Claims 1 and 2, and Claims 6 to 8, which relate

- to pharmaceutical compositions comprising the compounds of Claims 1 to 5,
- to a process for the preparation of these compounds, and
- to these compounds for use in the treatment of peripheral vascular disease,

are based on the same inventive concept and derive their patentability from that of Claims 1, 2, and 5.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: **The Chairman**

E. Görgmaier K. Jahn