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Aktenzeichen / Case Number / N° du recours : T 7/86

Anmeldenummer / Filing No / N° de la demande : 79 850 091.4

Veröffentlichungs-Nr. / Publication No / N° de la publication : 0 011 609

Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : Xanthine derivatives and pharmaceutical preparations containing these derivatives for use in the treatment of chronic obstructive airway disease and cardiac disease

Klassifikation / Classification / Classement : A 61 K 31/52

ENTSCHEIDUNG / DECISION

vom / of / du 16 September 1987

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent / Titulaire du brevet : Aktiebolaget DRACO

Einsprechender / Opponent / Opposant : Napp Laboratories Limited

Stichwort / Headword / Référence : Xanthines/DRACO

EPÜ / EPC / CBE Articles 54(5), 56

Kennwort / Keyword / Mot clé : "Novelty - of a specific compound from a generic formula - first medical use"
"Inventive step - choice from numerous possibilities"

Leitsatz / Headnote / Sommaire

A class of chemical compounds defined only by a general structural formula having at least two variable groups does not specifically disclose each of the individual compounds which would result from the combination of all possible variants within such groups (following decisions T 12/81 O.J. 1982, 296 and T 181/82 O.J. 1984, 401 at 410).

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 7/86

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 16 September 1987

Appellant : (Opponent)
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Decision under appeal : Interlocutory decision of Opposition Division of the European Patent Office dated 21 October 1985 concerning maintenance of European Patent No. 11 609 in amended form.

Composition of the Board :

Chairman : K. Jahn
Members : J. Arbouw
G. D. Paterson

Summary of Facts and Submissions

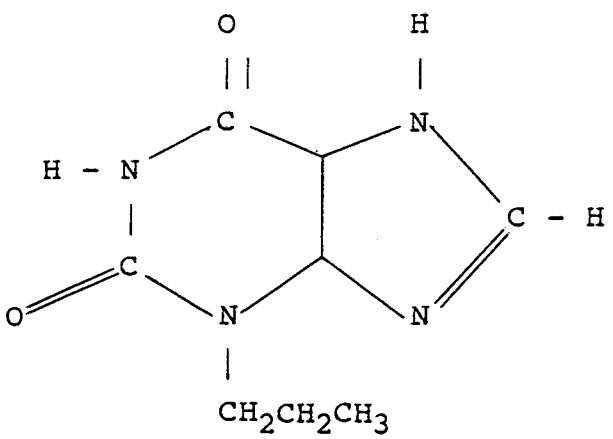
I. European patent No. 11 609 incorporating 4 claims was granted to the Respondents on 13 April 1983 on the basis of European patent application No. 79 850 091.4, filed on 28 September 1979 and claiming a priority of 21 October 1978 (SE 7 810 946).

II. The Appellants filed opposition to the grant on 9 January 1984 on the basis of new documents, and requested that the patent be revoked in its entirety on grounds of lack of novelty and inventive step.

III. By its interlocutory decision of 21 October 1985 the Opposition Division maintained the patent in an amended form, incorporating 2 claims.

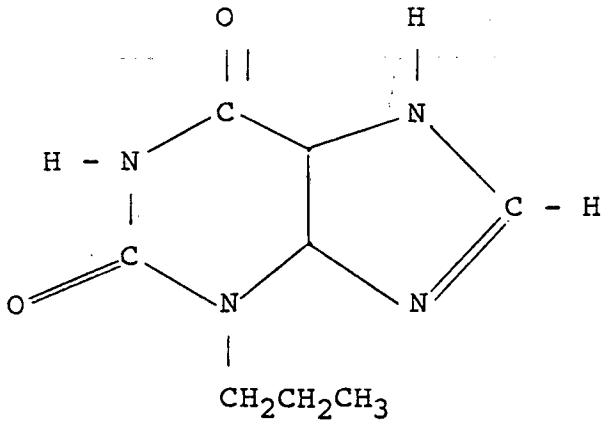
The independent Claims 1 and 2 read as follows:

"1. A pharmaceutical preparation for use in the treatment of chronic obstructive airway disease or cardiac disease comprising as active ingredient an effective amount of a compound of the formula



or a therapeutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier

2. A compound of the formula



or a therapeutically acceptable salt thereof, for use in the treatment of chronic obstructive airway disease or cardiac disease."

IV. The decision to maintain the patent as amended was based on the finding that the subject-matter of both claims is novel with respect to the cited documents. In particular, 3-propylxanthine is disclosed in Bull. Chem. Soc. Jap., 1973, Vol. 46, pages 506-509, (a document cited in the patent) but no pharmalogical data or use is given therefor.

It was further considered that an inventive step is present over the closest prior art, represented by documents (12) and (13) (see the list in paragraph VII below), in which 3-methylxanthine is disclosed, in particular because 3-propylxanthine (enprofylline) has considerably fewer side effects than 1,3-dimethylxanthine (theophylline).

V. A Notice of Appeal was filed by the Appellant against this decision on 17 December 1985, and the appeal fee was paid. A Statement of Grounds of Appeal was filed on 15 February 1986.

The submissions of the Appellant run essentially as follows:

The subject-matter of the patent-in-suit is obvious because the skilled man would expect enprofylline qualitatively to possess the same activity as that known for 3-methylxanthine: enprofylline was therefore an obvious candidate to test. Furthermore:

(i) it is not clearly apparent that 3-methylxanthine has similar side-effects to theophylline; and

(ii) it is questioned whether enprofylline has fewer side-effects than theophylline, rather it is suggested that the two compounds possess different patterns of side effects.

Furthermore, the subject-matter of the patent-in-suit is not novel, because document (20) discloses the diuretic use of enprofylline.

VI. The Respondent filed a response to the Appellant's Statement in which he argued that the problem underlying the invention is not only to make available a compound having favourable bronchodilator and cardiac potency in comparison with theophylline, but a compound which has a combination of these favourable activities without the unfavourable side-effects of theophylline.

He submitted that the choice of enprofylline for solving this problem was not obvious since the nearest structurally related compound, i.e. 3-butylxanthine was known to be a strong diuretic (see document (9), page 4, Table I and page 6, Table II).

VII. During the appeal proceedings, the parties based their arguments on the following documents:

(1) Johannesson, N. et al.: Relaxation of lower esophageal sphincter, and stimulation of gastric secretion and diuresis by antiasthmatic xanthines. Role of adenosine antagonism. Am. Rev. Resp. Dis. in press.

(2) Andersson, K-E. et al: Increase in plasma free fatty acids and natriuresis by xanthines may reflect adenosine antagonism. Eur. J. Clin. Pharmacol. 26, 33-38, 1984.

(3) Persson, C.G.A. et al.: Adenosine antagonism, a less desirable characteristic of xanthine asthma drugs? Acta Pharmacol. et Toxicol. 49, 317-320, 1981.

(4) Armitage, A.K. et al.: Structure-activity relationships in a series of 6-thioxanthines with bronchodilator and coronary dilator properties. Brit. J. Pharmacol. (1961), 17, 196-207. (This reference is not enclosed).

(5) Armitage, A.K. et al.: 1,3-Dialkyl-6-thioxanthines: a new series of bronchodilators and coronary vasodilators. Nature, No. 4756, 1107-1108, Dec. 1960.

(6) Lunell, E. et al.: Intravenous enprofylline in asthma patients. Eur. J. Respir. Dis. 65, 28-34, 1984.

(7) Lunell, E. et al.: A novel bronchodilator xanthine apparently without adenosine receptor antagonism and tremorogenic effect. Eur. J. Respir. Dis. 64, 333-339, 1983.

(8) Persson, C.G.A. et al.: Seizure activity in animals given enprofylline and theophylline, two xanthines with partly different mechanisms of action. Arch. Int. Pharmacodyn. Ther. 258, 267-282, 1982.

(9) Kattus et al.: Bull. John Hopkins Hosp., 1951, 89, pages 1-18

(12) Persson et al.: Actua Pharmacol. Toxicol., 1977, 40, pages 529-536

(13) Williams et al.: Biochemical Pharmacology, 1978, 27, pages 1545-1550

(14) Ing, Progr. During Res., 1964, 7, pages 305-30??

(17) Lunell et al.: Eur. J. Clinical Pharmacol., 1982, 22, pages 395-402

(18) Laursen et al.: Brit. J. Clinical Pharmacol., 1984, 18, pages 591-595

(19) Andersson et al.: Eur. J. Respir. Dis. Suppl., 1980, 61, pages 18-23

(20) Chem. Abstr., 1974, 81, 152277

(21) Laursen et al.: Eur. J. Respir. Dis., 1984, 65, pages 504-508

(22) A double-blind dose-finding study on oral enprofylline in patients with chronic obstructive airways disease

(23) Proc. of a symposium in Copenhagen, Exerpta Medica, 1985, pages 156-158

(24) Ibid., pages 477-480

(25) JP-A-7 404 469 (translation into English)

VIII. The Appellant requests that the decision under appeal be set aside and that the patent be revoked.

The Respondent requests that the appeal be dismissed and that the patent be maintained on the basis of Claims 1 and 2 as submitted to the Opposition Division.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. There is no formal objection to the current version of the claims, since they are adequately supported by the original documents. Claim 1 is based on Claim 5 as filed and Claim 2 of the patent as granted. Claim 2 is based on Claim 1 as filed and Claim 4 of the patent as granted.

3. In the view of the Board, the closest prior art is represented by document (12). This document discloses that 1,3-dimethylxanthine (theophylline) and its metabolite 3-methylxanthine are known to have bronchodilator activity and that the former is widely used in the treatment of obstructive airway disease (see page 534, last paragraph). Document (12) further discloses that theophylline is more potent than 3-methylxanthine (see page 531, Table 1; page 533, second paragraph and page 535).

In the light of this document, and in view of the fact that 3-methylxanthine has not actually been proposed as a medicine in the therapy of chronic obstructive airway disease, it appears not to be sensible to use this compound as the starting point for an attack on the ground of obviousness, as is suggested by the Appellant. This view is also independently supported by the authors of document (18) who used theophylline as a standard for comparing the pharmacological activity of enprofylline.

However, this document does teach that theophylline causes certain serious side-effects, particularly seizures or convulsions which may lead to death (see the description, page 2, line 11) and CNS-stimulating activity resulting in restlessness and tremor, which must be considered as a drawback in the therapy of chronic obstructive airway disease.

4. The technical problem underlying the invention with respect to document (12) is, therefore, making available a pharmaceutical preparation for use in the treatment of chronic obstructive airway disease, which is at least as effective as theophylline but does not cause the above adverse side-effects.

In order to solve this technical problem the Patentees propose 3-propylxanthine (enprofylline) for use in the treatment of chronic obstructive airway disease or cardiac disease.

4.1 The Board is satisfied that this technical problem has been solved. Documents (7), page 337, last three lines; (8), Abstract; and, (17), page 400, right hand column, lines 24-28, all published after the application date, prove that enprofylline is four to five times more potent as a bronchodilator than theophylline. Other subsequently published documents as set out below contain evidence that enprofylline not only lacks the above-mentioned serious disadvantages but additionally has considerably fewer side-effects, e.g. diuretic and gastric secretory action, tremorgenic effect.

See, for example the following documents:

(1) page 13, lines 19-23, Figs. 4 to 7;
(2) page 37, right column, second paragraph;
(3) page 319, footnote;
(6) page 29, left column, first paragraph, page 33, left column, last paragraph;
(7) the Abstract, page 338;
(8) page 276, lines 30-34;
(17) page 400; and,
(18) page 594, right column, lines 21-34.
(24) page 480, second paragraph.

4.2 The Appellant submitted that enprofylline has some other side-effects to a greater degree than does theophylline, notably a tendency to induce headache and nausea (see (18), page 594, right column, lines 46-58).

However, in chronic therapy these drawbacks would be of minor importance, since there is evidence (see (22), last lines and (23), page 157, lines 16-21) that they only occur during the first treatment week and that tolerance develops within a few days. Therefore these additional side-effects do not establish that the problem underlying the invention is not solved.

5. Examination of the cited prepublished documents has revealed that this technical teaching is not disclosed there. Consequently, the subject-matter of Claim 1 of the patent-in-suit is novel having regard to the prior art.

5.1 The Appellant alleged that document (20) describes the use of inter alia 3-propylxanthine as a diuretic, and suggested that this was a prior disclosure of the use of 3-propylxanthine for a method of treatment of the human or animal body by therapy, such as to deprive Claims 1 and 2 of novelty having regard to Article 54(5) EPC. Document (20) was not relied on before the Opposition Division, but will be considered by the Board under Article 114(1) EPC. The relevant part of the disclosure of document (20) is as follows: "Xanthines I (R = Me, Et, Pr, Bu, lower alkyl, R_1 = H, lower alkyl), which are useful diuretics, were prepared by ...".

Document (20) in fact discloses di-substituted xanthines wherein the substituents have to be chosen from two different lists. These lists comprise H and lower alkyl for position 8 and Me, Et, Pr, Bu and lower alkyl for position 3.

In its decision T 12/81 (Diastereomers, O.J. 1982, 296) the Board stated by way of obiter dictum that if two classes of starting substances are required to prepare a product and examples of individual entities in each class

are given in two lists of some length, then a substance resulting from the reaction of a specific pair from the two lists can nevertheless be regarded as new (see in particular, paragraph 13). In the Board's view, this principle is clearly applicable not only for starting substances in chemical reactions but also for polysubstituted chemical substances where the individual substituents have to be selected from two or more lists of some length, such as in the present case. Therefore, on this basis, document (20) cannot be interpreted either as a specific disclosure of 3-propylxanthine or consequently of a pharmacological use (as a diuretic) of this compound. Thus, in the Board's judgement, document (20) cannot be regarded as being detrimental to the novelty of the subject-matter of the claims.

In the application of this principle in a previous case, the Board has refused to regard those compounds, which result from the reaction of one compound arbitrarily selected from a group of generically defined reactants with a single reaction partner, as being prior disclosed. Thus, N-propyl-2.2.4.4-tetrametnyl-7-oxa-3.20-diaza-21-oxo-dispiro[5.1.11.2]heneicosane was considered to be novel since this compound (in contrast to the N-methyl compound) was not regarded as being disclosed merely by the description of the reaction of 2.2.4.4-tetrametnyl-7-oxa- 3.20-diaza-21-oxo-dispiro[5. 1.11.2]heneicosane with one of the groups of compounds, C_1-C_4-alkyl bromides (cf. T 181/82 O.J. 1984, 401, 410). But if a mere precisely structurally defined (described by a chemical reaction) class of chemical compounds with only one generically defined substituent does not represent a prior disclosure of all the theoretical compounds encompassed by an arbitrary choice of a substituent definition, it must

be clearly valid for a group of chemical substances, the general formula of which has two variable groups. Therefore, in the present case, a class of chemical compounds, defined only by a general structural formula having at least two variable groups does not specifically disclose each of the individual compounds which would result from the combination of all possible variants within such groups.

5.2 Document (20) is an abstract of document (25), which was referred to by the Respondent.

Document (25) deals with a process for the preparation of 3-alkyl substituted xanthines; it is stated (with reference to a US-patent specification) that 3-substituted xanthines are superior in diuretic action, for example to theophylline and (with reference to an article in "Biochemistry") that such compounds are "useful compounds for use in test and studies of biochemistry and pharmacology or in the preparation of medicines." (See document (25), page 2, last paragraph). The preparation of 3-n-propylxanthine is described in Example 3, by means of the claimed process.

In the Board's opinion this general statement of the possible use of a large class of chemical substances is not a specific disclosure of the medical utility of every individual entity within that class.

Therefore, in the Board's judgement, document (25) cannot be regarded as being detrimental to the novelty of the pharmaceutical use of 3-propylxanthine.

6. It still remains to be examined whether the requirements for inventive step are met by the subject-matter claimed. It was, in fact, known from the prior art that 1,3-di-substituted xanthine derivatives possess potent bronchodilator and coronary dilator properties (see e.g. documents (4), (5), (12) and (13)). Only one monoalkyl-xanthine, i.e. 3-methylxanthine, has been disclosed in the cited prior art as having bronchodilator and coronary dilator activity (see (12) and (13)).

In these papers the pharmacological activity of 3-methylxanthine is compared with that of theophylline. Document (12) (see page 535, lines 5-7) describes that theophylline is always more potent (1 to 5 times) than 3-methylxanthine, whereas document (13) (see page 15-18, last paragraph) describes that 3-methylxanthine and theophylline have approximately equal effects.

From these documents it can be concluded that theophylline is at least as potent as 3-methylxanthine, and that theophylline is the nearest compound in the prior art which is actually used in the therapy of obstructive airway disease (see (12), page 534, last paragraph).

Therefore, as indicated under 3 above, theophylline is in fact the nearest prior art and can be used as a standard for comparison.

6.1 The Appellant argued that, given the fact that 3-methylxanthine was known to have pharmacological activity, it would have been natural and logical to consider simple higher alkyl analogues thereof for further investigation. This line of argument, besides disregarding at least one aspect of the problem addressed (i.e. making available a

pharmaceutical without the above-mentioned serious side-effects), fails to take into account that the man skilled in the art has an immense number of substituted xanthines to choose from and that the trend in the prior art is in a different direction, i.e. the use of 1,3-dialkylxanthines and 1,3-dialkylthioxanthines (see (4), e.g. Table 1 and (5)). Documents (12) and (13) only deal with 3-methylxanthine since this compound is a known metabolite of theophylline (see e.g. (12), the Abstract), and as such will have some effects when theophylline is used in therapy (see (12), page 536, first lines and (13), page 1549, second half of the left column).

6.2 The second question with regard to inventive step is: was it obvious for the man skilled in the art to choose enprofylline from the great number of possible xanthine-derivatives, as a compound which has less seizure activity and CNS-stimulating activity and moreover has less diuretic activity?

6.3 The Board is not aware of any facts which would allow the inference to be drawn that choosing enprofylline from the immense number of substituted xanthines would provide an improved medicine for use in the treatment of chronic obstructive airway disease which has less seizure activity and CNS-stimulating activity. Nor did the appellants submit any such facts that would indicate this. The arguments based on this assumption, therefore, cannot stand. The Board consequently concludes that the solution offered by the patent to the existing problem posed was not suggested by the cited state of the art and must be regarded as the result of an inventive step.

6.4 Moreover, it is, in fact, known (see document (9), Tables I and II) that many substituted xanthine derivatives have strong diuretic activity. One of the strongest diuretics described in (9) (see Table II) is 3-butylxanthine, the compound which is structurally the most closely related compound to enprofylline which is described in the art. This teaching will not suggest to the man skilled in the art, seeking a solution to the above stated problem that enprofylline is a suitable candidate among the great number of substituted-xanthines.

In fact, the man skilled in the art would have expected that enprofylline would possess diuretic activity; this is not apparently in fact the case, having regard to the evidence provided by the Patentees (see (1), page 13, lines 3-8 and Figures 4 and 5 and (2), page 37, right column, second paragraph).

6.5 The Board is bound to say that in seeking to analyse retrospectively how a skilled person might have been able to arrive at the concept of the invention by arbitrary selection of one out of many possible xanthines, the Appellant is adopting a typical ex post facto approach which fails to do justice to the objective standards by which inventive step is to be assessed. The consistent case law of the Board requires that the question of obviousness be considered from the viewpoint of the existing technical problem. The Appellant has not sought to argue from this viewpoint, nor is a technically sound line of reasoning evident to the Board from its own knowledge of the field that would enable a skilled person to solve the problem here being addressed making available a compound for use in the therapy of chronic airway disease not possessing the serious side-effects such as seizures, convulsions and CNS-stimulating activity.

6.6 The assessment of inventive step is related to the choice of a particular xanthine for application in the therapy of chronic airway disease. The proper question in this regard is not whether the skilled man could have chosen enprofylline, but whether, from the starting point of the closest prior document, he would have done so in the expectation of solving the technical problem addressed (see Decision T 2/83, "Simethicone Tablet/RIDER", O.J. 1984, 265, 271, para. 7).

6.7 For the reasons given above, in view of the problem underlying the claimed method, the Board considers that the prior art cited and the common general knowledge did not provide any indication that the choice of enprofylline from the numerous available xanthines, would solve the technical problem underlying the invention. Thus the subject-matter of the patent-in-suit as defined in the Claims 1 or 2, is considered to involve an inventive step.

Order

For these reasons, it is decided that:

The appeal is dismissed.

The Registrar: The Chairman: