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Aktenzeichen / Case Number / N° du recours : T 164/83

Anmeldenummer / Filing No / N° de la demande : 80 104 372.0

Veröffentlichungs-Nr. / Publication No / N° de la publication : 23 350

Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : Theophylline derivatives, a process for preparation of the same and a therapeutic composition

Klassifikation / Classification / Classement : C 07 D4 73/08

ENTSCHEIDUNG / DECISION

vom / of / du 17 July 1986

Anmelder / Applicant / Demandeur : EISAI CO., LTD

Patentinhaber / Proprietor of the patent /
Titulaire du brevet :

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence : Antihistamines/EISAI

EPÜ / EPC / CBE Art. 52(1) and 56 EPC
"Inventive step" "Quantitative improvement"
"Technical progress", "Comparative tests",
"Novelty of selection", "Experiments with animals".

Leitsatz / Headnote / Sommaire

I. Technical progress shown in comparison with marketed products as an alleged support for inventive step cannot be a substitute for the demonstration of inventive step with regard to the relevant closest state of the art. (Following T 181/82 "Spiro-Compounds"/CIBA-GEIGY, OJ 9/1984, 401).

II. The possibility of a prohibition of experiments with animals in one Contracting State of the EPC is not a sufficient reason for declining the submission of test results in comparison with the closest state of the art if the inventive step can only be demonstrated in this manner.

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Case Number : T 164 /83

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 July 1986

Appellant : EISAI CO., LTD
6-10, Koishikawa
Bunkyo-ku
Tokyo
Japan

Representative : Hansen, Bernd, Dr.rer.nat.
Hoffmann, Eitle & Partner
Patentanwälte
Arabellastrasse 4
D-8000 München 81

Decision under appeal : Decision of Examining Division 008 of the European Patent Office dated 27 May 1983 refusing European patent application No 80 104 372.0 pursuant to Article 97(1) EPC

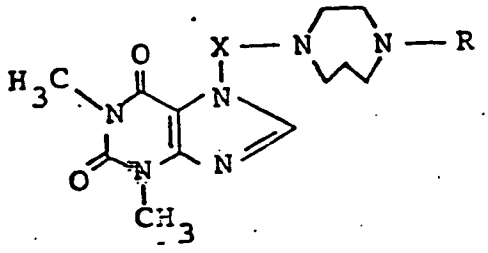
Composition of the Board :

Chairman : P. Lançon
Member : G. Szabo
Member : R. Schulte

Summary of Facts and Submissions

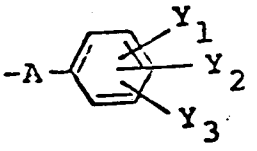
I. European patent application No. 80 104 372.0 filed on 24 July 1980 and published on 4 February 1981 with publication number 23 350, claiming priority of the prior application on 25 July 1979 (JP-93 635/79) was refused by the decision of the Examining Division 008 of the European Patent Office dated 27 May 1983. The decision was based on claims 1 to 7 received on 29 June 1982. Claims 1 and 7 were worded as follows:

1. A theophylline derivative having the general formula:



and pharmacologically acceptable acid addition salts thereof, wherein X is $-(CH_2)_n-$, in which n is an integer of 1 to 6, or $CH_2 - \underset{\underset{OH}{|}}{CH} - CH_2-$:

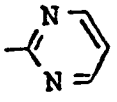
and R is a C_1 to C_6 alkyl;

a group having the formula 

wherein A is $-(CH_2)_m-$, in which m is an integer of 0 to 2, $\overset{\overset{O}{\|}}{-C-}$, $-\underset{\underset{CH_3}{|}}{CH}-$ or $-CO - CH = CH -$, and Y_1, Y_2 and Y_3, which can be the same or different, each is hydrogen, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylsulfonyl, halogen or nitro;

a group having the formula - Z - OH, in which Z is $-(CH_2)_a-$, in which a is an integer of 1 to 3, or $- CH_2 - \underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}} -$;

a group having the formula $-COR_1$, in which R_1 is hydrogen or C_1 to C_6 alkyl; or



7. Therapeutical composition, having antihistaminic and vasodilating activity, characterised by a content of at least one compound according to any of preceding Claims 1 - 3 and pharmacologically acceptable auxiliary agents.

II. The stated ground for the refusal was that the subject-matter of Claims 1 to 3 and 7 did not involve an inventive step with regard to

(A) GB-A-1 289 287

(B) GB-A-1 133 989, and

(C) Chem. Abstr. 1977, 86, 89761 v.

The cited documents, particularly (A) and (C) disclosed theophilline derivatives which have vasodilating and/or antihistaminic acitivity, with a structure similar to those of the compounds in the application. Although the applicant had demonstrated high antihistaminic activity in comparison with three commercially known agents for the purpose, he failed to show any surprising improvement vis-à-vis the structurally closest state of the art. The antihistimanic activity of the compounds in the application was therefore not unexpected and the compounds were considered as obvious.

III. The applicant lodged an appeal against the decision on 18 July 1983 with payment of the fee, and submitted a statement of grounds on 8 September 1983. After a communication from the Board, an oral hearing was held on 17 July 1986.

IV. The appellant submitted in the statement of grounds and during the proceedings substantially the following arguments:

(a) The new compounds were distinguished by remarkable pharmacological properties, including high activity, low toxicity and an impressive vasodilating action. Their superiority over known drugs was demonstrated. The comparison with the structurally closest compound specifically disclosed in (A) was unfair, since this was not available and was not on the market, and was also unjustified in view of the more relevant comparisons already disclosed in the specification.

(b) It was illogical to rely on comparative tests with structurally close known compounds, since no proper structure/activity relationship existed in this field, and any modification of the molecule would have brought about a surprising result. Because of this, the surprising superiority over recognised good agents was more relevant evidence in respect of the inventive step, since it represented a real enrichment of the art.

(c) The German decision in the "Anthradipyrazol" case (GRUR, 70, 408) gave guidance as to the selection of comparative compounds to show technical superiority. Its conclusions were still valid under the new law and

relevant to the present case. Improvements over the marketed good agents for the relevant purpose also implied that this would be the case in comparison with a compound merely disclosed in a document.

(d) Tests demanded by the Office would be very costly and require experiments on animals. In view of certain legal provisions in Germany, a German firm would not be allowed to carry out such investigations. A Japanese applicant should not be placed in a worse position than a German one, and be compelled to do such tests in the circumstances.

V. The appellant requests that the impugned decision be set aside and that a European patent be granted on the basis of the following documents:

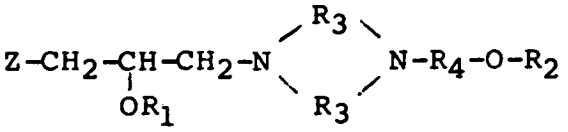
(a) Claims 1 to 7, submitted on 29 June 1982, and
(b) a description adapted thereto. Furthermore, he declared his willingness to carry out comparative experiments which were considered necessary by the Board.

Reasons for the Decision

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

2. There can be no formal objection to the current version of the claims since it is adequately supported by the originally filed documents. Claim 1 has been amended so as to replace the term lower with "C_1 to C_6" in accordance with the disclosure on page 2, lines 21 to 29.

3. The closest prior art, GB-A-1 289 287 (A) describes theophylline derivatives having the general formula



in which Z is a 1,3-dimethyl-xanthine or, a 3,7-dimethyl-xanthine group, substituted at the 7-position or on the 1-position, respectively, R_1 and R_2 are the same or different and each represents a hydrogen atom or an aliphatic, cycloaliphatic, heterocyclic or aromatic acyl group, with the proviso that if Z is 1,3-dimethyl-xanthine, only one of R_1 and R_2 is a hydrogen atom, R_3 is an alkylene group containing 2 or 3 C atoms, and R_4 is an alkyline group containing 2 to 4 C atoms; together with salts of compounds of the general formula.

Most of the Examples in document (A) illustrate piperazino-derivatives of 1,3- or 3,7 dimethyl-xanthine. Example 38.2, however, describes the preparation of 1-[3-N(N'-ß-hydroxyethyl-1,4-diaza-cycloheptano-2-hydroxy)]-propyl-3,7-dimethyl-xanthine, which is a 'homopiperazino'-derivative. The compounds according to document (A) exhibit a coronary-dilatative effect with simultaneous central depressive or relaxant properties. Their spasmolytic effect against histamine is strongly apparent. They have a comparatively low toxicity (see page 3, lines 20 to 55).

4. Given this state of the art the technical problem was to provide other compounds showing a pharmacological property at the same or at an increased level. The solution of the problem was the provision of 7-theophyllinyl derivatives wherein the substituent also characteristically includes a homopiperazino group. That such compounds exhibit antihistaminic activity can be seen from the tabulated test results from Table 1, samples 4 to 11, on pages 13 and 14 of the specification. Although the group claimed in the application overlaps to a small extent with the broad group defined in (A), it embraces no specifically disclosed

compounds from (A). Provided also that the overlapping area represents a proper selection, which means that it is more than an arbitrarily chosen sample from (A) having merely the same kind of properties and capabilities as the prior art ("Thiochloroformates/HOECHST, T 198/84, OJ 7/1985, 209 and 214), the novelty of the common area could be recognised. The embodiments of Claim 1 which fall outside (A) are not disclosed specifically or generically in any cited document since none of them refers to a homopiperazino group attached to the 7th position of theophylline. The issue is therefore that of the inventive step.

5. The claimed subject-matter in the present application basically differs from the closest specific compound disclosed in Example 38.2 of (A) by having the substitutions of theophylline at positions 1 and 7 reversed. The nearest compound to this art in the present application is additionally distinguished by having no hydroxy group in the propyl chain linking the homopiperazino group to the aromatic ring system (cf. p.3, lines 19-20). The question arises whether the antihistaminic or vasodilating activity of such compounds was foreseeable in view of the cited art.

6. In view of the closeness of at least some of the compounds in the application under appeal to those in (A), there must be an expectation of the qualitative retention of the same activities at least to the same or to a somewhat lesser degree. The specific choice of the 7th position on theophylline is also within the scope already envisaged in (A), where both the 1st and 7th positions are available for the same kind of substitution without affecting the basic capabilities of the compounds. As far as the overlap is concerned the presumption is directly supported by the general statements in the cited document. Unless evidence refutes this assumption by showing that the small shift in structure to the claimed area was unexpectedly associated

with a significant improvement in the property relevant to the solution of the stated problem, the presumption prevails that the compounds represent only predictable effects and are therefore obvious. The onus is on the applicant to refute this inference based on the information so far available. If he chooses to give evidence by comparative tests, these must be carried out in respect of the relevant closest state of the art (cf. "Spiro Compounds/CIBA-GEIGY, T 181/82, OJ 9/1984, 401).

7. The relevant question is whether the skilled person having studied the closest state of the art and being guided by the technical problem would have been aware from his common general knowledge and also from his familiarity with related art what kind of modifications of that art could make the desired properties and effects available. It is irrelevant if his claimed solution of the problem is unforeseeable on the basis of less close or structurally remote prior art, as long as it is derivable, together with the required function, from some other, more relevant known compound, which is, for this very reason, termed as the "closest" state of the art. A compound lacking inventive step over certain disclosures in the state of the art cannot be rendered patentable in view of non-obviousness over other disclosures. This is why the unexpected results of the submitted comparison with structurally unrelated drugs were irrelevant in the present case.

8. The headnote of the "Anthradipyrazol" decision in Germany reveals (GRUR, 1970, 408) that this case was concerned with "technical progress" (technischer Fortschritt) as a "criterion of patentability" under the old law in that country. In any case, the cited decision required a separate comparison with all similarly acting compositions for the purpose, except in the case when the proven superiority over one outstanding agent also implied a substantial improvement

over the rest of them. In the present case there is no possibility to infer from the results available so far that superiority is also given in comparison with the relevant closest prior art, i.e. the compound of Example 38.2 of (A). That a compound is not marketed at a particular time may have many reasons - it cannot be interpreted as a sign of inferiority in any respect.

This requirement for technical progress in the general sense was basically independent from the inventive step since any application could be rejected for lack in one respect or the other separately. No such criterion for patentability exists under the EPC. It is true, of course, that technical superiority might be indicative of the inventive step if it specifically relates to the solution of the problem arising in respect of the closest state of the art. It is, therefore, the view of the Board that technical progress shown in comparison with marketed products, as an alleged indication of the inventive step, cannot be a substitute for the demonstration of inventive step with regard to the relevant closest state of the art. (Following T 181/82 "Spiro-Compounds"/CIBA-GEIGY, OJ 9/1984, 401).

9. The argument about the costly character of the comparative tests are not persuasive either. Whether or not the structural modifications of the state of the art are associated with an improvement at all is a fundamental aspect of the inventive step. Whether or not in a particular country experiments on animals may also be problematic under national law cannot be taken into consideration either, since this or similar difficulties could arise in connection with the testing or development of any invention or some ground or another in various countries of the world, and no special considerations could apply to applicants of various nationalities on such grounds.

10. The Board has therefore come to the conclusion that the possibility of a prohibition of experiments with animals in one Contracting State of the EPC is not a sufficient reason for declining the submission of test results in comparison with the closest state of the art if the inventive step can only be demonstrated in this manner. The requirement for the comparative tests, which necessitates the use of animals in the present case according to the appellant, could only be waived if the Board had been in a position to recognise the inventive step on the basis of other relevant facts. No such evidence has been submitted in relation to the closest state of the art.

11. In view of the above, the solution of the problem of merely providing compounds with antihistaminic activity did not involve an inventive step. As indicated by the Examining Division, no surprising improvement has yet been demonstrated, which would be indicative of an inventive solution of the more difficult technical problem of providing a significantly improved antihistaminic effect. In view of the appellants offer to submit such evidence if the Board were unable to recognise an inventive step without it, it was indicated at the oral hearing that an opportunity will be given to present this to the Examining Division so that the substantive examination could be continued on that basis.

Order

For these reasons it is decided that:

1. The impugned decision is set aside.

2. The application is remitted to the Examining Division for further prosecution. The applicant has to submit test results comparing the claimed properties (cf. Claim 7) of the compound described on page 3, lines 19 and 20 of the application with those of Example 38.2 of GB-A-1 889 287 (page 10, lines 24-26) until 31 January 1987.

The Registrar: The Chairman:

J. Rückerl P. Lançon