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D E C I S I O N
of 23 August 1994

Case Number: T 0964/92 - 3.3.1

Application Number: 88116669.8

Publication Number: 0307970

IPC: C07D 319/20

Language of the proceedings: EN

Title of invention:

1,4-Benzodioxane derivatives, process for preparing them,
pharmacological composition and use

Applicant:

Eisai Co., Ltd.

Opponent:

-

Headword:

Benzodioxane derivatives/EISAI

Relevant legal norms:

EPC Art. 56

Keyword:

"Inventive step (no - obvious alternative)"

"Common general knowledge"

"Identification of the technical problem and the closest state
of the art"

Decisions cited:

T 0334/92, T 0060/89, T 0439/92, T 0164/83, T 0181/82,
T 0024/81, T 0220/84

Catchword:

The question as to what extent a chemical structure can be modified without causing major changes in its biological activity is equally relevant to the question as to whether or not it is credible that all members of a certain group of chemical compounds solve a particular technical problem, e. g. whether they can be fairly assumed to be useful in a therapeutical treatment, and to the question of whether or not such an activity can be expected on the basis of the state of the art. If the answer to the former question can only be yes with respect to considerations forming part of the common general knowledge, then the question whether or not the solution of the same technical problem by providing the same group of compounds was obvious must be answered on the basis of the same considerations (No. 2.8. of the reasons).

Case Number: T 0964/92 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 23 August 1994

Appellant: Eisai Co., Ltd.
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Decision under appeal: Decision of the Examining Division of the European Patent Office dated 22 May 1992 refusing European patent application No. 88 116 669.8 pursuant to Article 97(1) EPC.

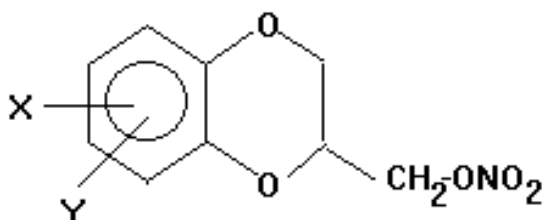
Composition of the Board:

Chairman: A. Jahn
Members: R. K. Spangenberg
J. A. Stephens-Ofner

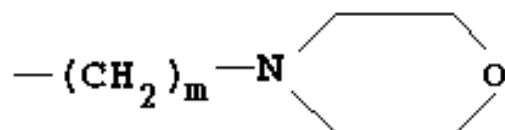
Summary of Facts and Submissions

- I. European patent application No. 88 116 669.8 was filed on 7 October 1988 as a divisional application of European patent application No. 86 110 080.8 filed on 22 July 1986 and was published under No. 0 307 970. On 22 May 1992 the Examining Division refused the application. On 22 July 1992 an appeal was filed against this decision and the appropriate fee was paid on the same date.
- II. The decision under appeal was based on two sets of claims, filed on 23 November 1990, the first set comprising 6 claims for the Contracting States other than AT and the second 3 claims for AT. Claim 1 of the first set read as follows:

"A 1,4-benzodioxane derivative represented by the following general formula:



wherein X and Y are the same or different, and each represent a hydrogen atom or a group represented by -OR in which R denotes a hydrogen atom, a lower alkyl, a lower alkoxy carbonyl or acyl group or a group represented by the formula

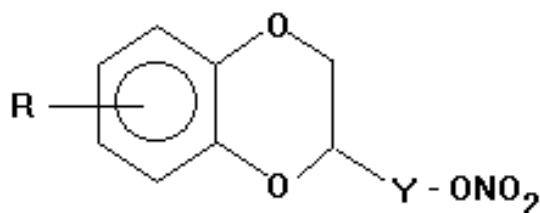


in which m is 1 or 2; cyano group; or carboxy group; exclusive of the case wherein X=Y=H, or a pharmacologically acceptable salt thereof."

The ground of refusal was that the application did not meet the requirement of Article 56 EPC, since the subject-matter of the above claim was obvious in the light of

(1) GB-A-1 027 967,

disclosing compounds of the general formula



wherein Y is, inter alia, a methylene group and R is hydrogen, chlorine, bromine or trifluoromethyl, and which compounds have vasodilator and hypotensive activity and are useful for the treatment of angina pectoris. The Examining Division considered that document (1) represented the closest state of the art and that, in view of Decision T 164/83, the technical problem could not be seen in providing compounds of a higher activity than the activities of commercially available medicaments for the treatment of angina pectoris, such as nitroglycerine (NG), isosorbide dinitrate (ISDN), or Nicorandil (N-2-nitratoethyl-nicotinamide), nor, in the absence of any evidence based on a direct comparison, in providing compounds having a higher activity than the activities of the compounds disclosed in document (1). The Examining Division further considered that the activity data contained in the application as filed did

not relate to a compound according to the above Claim 1. Thus the relevant technical problem was seen simply to provide compounds of a chemical structure and having a therapeutic activity similar to those of the compounds disclosed in document (1). The Examining Division found that a person skilled in the art, looking for such compounds, who was aware of the prior art acknowledged in the description, could reasonably have expected that all compounds having a nitratealkyl group, including those proposed in the present European patent application, would have this activity.

III. A Statement of Grounds of Appeal was received on 22 September 1992. In a communication pursuant to Article 11(2) of the rules of procedure of the Boards of Appeal the Board referred to

(2) E. Schröder et al., "Pharmazeutische Chemie (1982), p.711 and 712.

and expressed the view that this document might support the Examining Division's finding that those skilled in the art assumed that all esters of nitric acid would show therapeutic activity against angina pectoris.

Oral proceedings took place on 23 August 1994. In his Statement of Grounds of Appeal and during the oral proceedings the Appellant submitted that the technical problem that was solved by the compounds of the present patent application was to provide further compounds which are useful inter alia in the treatment of heart failure, and which show similar or improved pharmaceutical properties in comparison with those of the cited prior art. He argued that, in the field of

pharmaceuticals, small structural modifications could effect dramatical alterations with regard to the pharmaceutical properties (activity or toxicity). Therefore a skilled person would have been extremely reluctant to modify chemical compounds by exchanging substituents in existing compounds by other substituents not yet described in the prior art. In addition, a skilled person would not even have expected that compounds having the functional substituents defined in the present Claim 1 would have pharmaceutical properties similar to those of the compounds of document (1), since these substituents had a different chemical reactivity and different electron donor or acceptor properties. Therefore, the skilled person would not have considered the claimed compounds suitable for solving the above-defined technical problem. In addition, he submitted that non-obviousness already followed from the fact that document (1) was published about twenty years before the priority date of the present application, and had not, during this long period of time, encouraged those skilled in the art to develop structurally similar compounds. In any case, so he argued, it had already been decided in Decision T 334/92 of 23 March 1994 (allowing an appeal relating to the parent application) that this document was not a realistic starting point for assessing the inventive step.

- IV. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the claims submitted on 23 November 1990, i.e. the claims underlying the decision under appeal.

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

Reasons for the Decision

1. The appeal is admissible.
2. The only relevant issue of this appeal is the question of inventive step.
 - 2.1. In the Board's judgment the Examining Division correctly held that the object of the application was to provide further compounds having activity against angina pectoris, since the statement in the patent application as filed that this object was to provide compounds having a higher activity than some widely used medicaments for treating angina pectoris, such as NG or ISDN, cannot be taken into account in the absence of any evidence that it had been achieved.
 - 2.2. By contrast, in the parent case (see Decision T 334/92 of 23 March 1994, referred to by the Appellant), the application as filed did contain evidence showing that the object of providing compounds having a higher activity than that of NG or of ISDN had in fact been achieved. It was for this and no other reason that in the above decision the Board rejected the Examining Division's approach for assessing the inventive step on the basis of the quite different technical problem of modifying or improving the compounds of document (1) (see points 4.2 and 4.3 of the reasons). The Board accordingly held that the issue of inventive step could only be objectively dealt with if an artificial, mechanistic and therefore unrealistic approach was

avoided. It therefore found it inappropriate to formulate a technical problem which a skilled person would never have considered, and it therefore held that it was, in the circumstances of the case, not only necessary to determine the closest state of the art by reference to the chemical structure and to the technically useful properties of a particular item of prior art, but also to consider carefully whether or not in the specific circumstances of the case, and taking into account all available information about the technical context of the claimed invention, a person skilled in the art would have had any reason to select this piece of prior art as his basis for further development.

- 2.3. Thus the Appellant's submission that document (1) should not be considered as a realistic starting point for the determination of the relevant technical problem in the particular circumstances of the present case as well, cannot, for the above reasons, be based on the Board's considerations in Decision T 334/92. On the contrary, in the circumstances of the present case, where the skilled person sets out to seek no more than alternatives to known compounds being described as medicaments for treating angina pectoris, the Board holds that the skilled person would consider any compound or group of compounds belonging to the state of the art, and being known to have the desired activity as being a suitable starting point. In such a case the length of time for which this document has been available to the public, is therefore irrelevant. Thus there is no reason why document (1) which clearly describes compounds having a

high degree of structural similarity with the claimed ones, should not be regarded as the closest state of the art, and be it only for practical reasons (see e.g. T 439/92 of 16 May 1994, not intended for publication in OJ EPO, point 6.2.1 of the reasons).

- 2.4. Starting from this state of the art, the technical problem underlying the present application consists in providing further compounds having activity against angina pectoris, as already stated in point 2.1 above.

- 2.5. According to the present Claim 1 it is proposed to solve this problem by the 2-nitratomethyl-benzodioxanes of formula I, wherein the benzene nucleus of the benzodioxane ring system is substituted by cyano, carboxy or -OR groups replacing the chloro, bromo or trifluoromethyl substituents disclosed in document (1).

- 2.6. Although the application documents do not contain any test result showing that at least one of the group of compounds defined by formula I possesses the desired activity, the Board is satisfied that the above-defined technical problem is credibly solved by the claimed compounds, having regard to the common general knowledge reflected by document (2). This document provides an example for the widely accepted assumption that chemical compounds of similar structure normally have similar properties, including biological activity. Although the Board fully agrees with the Appellant's submission that there is a large number of cases where this assumption is not applicable, particularly in the realm of biological active compounds where small structural

modifications may sometimes cause dramatic changes in activity, it is nevertheless aware of another large number of cases where the skilled person was right to assume that small changes in the structure would only result in minor changes of the biological activity (see e.g. T 181/82, OJ EPO 1984, 401, No. 5 of the reasons, and T164/83, OJ EPO 1987, 149, No. 6 of the reasons). Were it otherwise, practically no claim to a group of chemical compounds comprising members which have never been synthesised or tested for a desired biological activity, including the present one, where no test result has been submitted, could be justified. It is therefore clear that the extent to which a chemical structure is to be regarded as being sufficiently similar to a known structure to suggest to a skilled person similar properties depends on the circumstances of each particular case. In the Board's judgment, it is therefore necessary to establish this extent by reference to documents in cases where it is in dispute. For this reason, the Board referred to the above document, reflecting the common general knowledge in respect of the structure-activity relationship for chemical compounds with activity against angina pectoris.

- 2.7. This document states that esters of nitrous acid, such as isoamylnitrite, esters of nitric acid, such as NG, as well as the anion of nitrous acid, but not the anion of nitric acid are active in the treatment of angina pectoris (see page 711, the first paragraph of Chapter 2.4.2). In other words, according to this document practically all esters of nitric acid must be

supposed to have the respective activity. This interpretation of the content of document (2) was disputed by the Appellant, who proposed instead to regard the above disclosure as being limited to the specific compounds mentioned in the table on page 712. However, such a narrow interpretation is arbitrary and therefore wrong and would, in the Board's judgment, conflict with the fact that the state of the art included other compounds having basically different chemical structures, such as nicorandil and the compounds of document (1). Moreover, the fact that the nitrite anion is among the active compounds would suggest that the esters mentioned might be "prodrugs" being capable of producing nitrite ions under physiological conditions.

The Appellant's interpretation of document (2) would, in addition, lead to the assumption that only very limited structural modifications would be possible without destroying the therapeutical effect of organic nitrate esters. The Appellant himself, however, has obviously inferred this therapeutical effect of the claimed compounds from the fact that the compound 8-hydroxy-2-nitratomethyl-7-nitro-1,4-benzodioxane, a compound which belongs to the subject-matter of the parent application and is not comprised by the present Claim 1, had been shown to be active. However, the structural differences between this compound and at least those compounds according to the present application which do not contain an -OR group are at least as great as the structural differences between the latter compounds and the compounds of document (1). Therefore the Appellant's

interpretation of the content of document (2) is also inconsistent with the way he had assessed the activity of the claimed compounds.

- 2.8. The question as to what extent the structure of a chemical compound can be modified without causing major changes in its biological activity, is equally relevant in respect of the question as to whether or not it is credible that all members of a certain group of chemical compounds solve a particular technical problem, in the present case whether they can be fairly assumed to be useful in the therapeutical treatment of angina pectoris, and to the question of whether or not such an activity can be expected on the basis of the state of the art. If the answer to the former question can only be "yes" with respect to considerations forming part of the common general knowledge, then the question whether or not the solution of the same technical problem by providing the same group of compounds was obvious must be answered on the basis of the same considerations, since in the Board's judgment the same common general knowledge must be taken into account in respect of all aspects of patentability (see also T 60/89, OJ EPO 1992, 268, point 3.2.5 of the reasons). It is thus not permissible that an applicant, who, as in the present case, has alleged the solution of the technical problem by a group of chemical compounds comprising individual compounds which have neither been synthesised nor tested for the desired biological activity, wishes, at the same time, to have any kind of structural modification with respect to the state of the art to be considered inventive. In other words, if the solution of the

underlying technical problem is only credible because it can be fairly assumed that compounds of similar chemical structure would to a certain extent have similar therapeutical activity, then the skilled person would consider the same kind of structure-activity relationship when looking for further compounds having the same activity. The Board is thus unable to agree with the Appellant's line of argument.

- 2.9. Although the Board would concur with the Appellant's submission that a skilled person would not consider substituents having chemical reactivities and electron donor or acceptor properties different from those proposed in the state of the art in cases where no specific information or common general knowledge about the structure-activity relationship exists, the Board is satisfied in the present case, that the skilled person would have expected, in the light of the common general knowledge discussed above, that the type of substitution in the benzene ring of the 2-nitratoalkyl-benzodioxanes is not important for the activity against angina pectoris and would therefore have been encouraged to replace the substituents mentioned in document (1) by any other pharmaceutically acceptable substituent, in order to solve the present technical problem. The Appellant's submission that the skilled person would not have considered the substituents mentioned in the present Claim 1 because it would have expected that their introduction would lead to toxic compounds which would not be pharmaceutically applicable was not supported by any evidence and is, in the Board's judgment, not in agreement with the common general

knowledge. On the contrary, it is beyond any reasonable doubt that substituents such as -OR or the carboxyl group are well known as being pharmaceutically acceptable substituents for a benzene nucleus, since they are present in such widely used medicaments as acetylsalicylic acid. For this reason the Board holds that the subject-matter of the present Claim 1 does not involve an inventive step, as required by Article 52(1) EPC.

- 2.10. During the oral proceedings the Appellant further submitted that on the above basis the skilled person would have had to consider a host of possible alternatives, and that in the absence of any hint in the prior art towards the suitability of the relative small group of compounds defined in the present Claim 1, the selection of this group was not obvious, since the skilled person would not have chosen just this group. However, this submission must be dismissed, since if, as in the present case, a number of reasonable structural modifications was obvious, all compounds resulting from such modifications, irrespective of their number, are equally suitable candidates for solving that technical problem and would therefore all be "suggested" to the skilled person. Any arbitrary choice among them does therefore not involve an inventive step (see e.g. T 220/84 of 18 March 1986, No. 7 of the reasons). An inventive step could, however, be present if it could be shown that the selected compounds achieve a particular technical result that would not be achieved by the other members of the broader suggested group of compounds (purposive selection). In the present case, however,

there is no indication of such an additional technical effect, nor has any been alleged to exist.

- 2.11. The Appellant further argued that the presence of an inventive step followed from the mere fact that document (1) was published about 20 years before the priority date of the present application and had never since been used as a basis for further development. This argument must likewise be dismissed, since the EPC does not provide for a limitation of the period of time during which a document belongs to the state of the art. Therefore a document which is 20 years old has of course to be considered in respect of the question of inventive step. The finding in Decision T 334/92, referred to by the Appellant, according to which such an old state of the art may disqualify in certain circumstances (which do not apply in the present case, see No. 2.3 above) as a starting point for assessing inventive step, in no way implies that it should not be considered at all. Nevertheless, the age of a document may be a circumstantial pointer to the presence of an inventive step. However, such a pointer can only be taken into account, by way of a subsidiary consideration, in a case where obviousness does not already follow from other reasons (see e.g. T 24/81, OJ EPO 1983, 133, No. 15). In the present case, therefore, having regard to the reason given in No. 2.9 above, there is no room for such a subsidiary consideration.
3. Claim 1 not being allowable, there is, in the absence of any request to this effect, no basis for considering the allowability of the other claims.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

E. Görgmaier

A. Jahn