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

Case Number: T 0334/92 - 3.3.1

Application Number: 86110080.8

Publication Number: 0210581

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 (yes) - closest prior art - determination of the technical problem"

Decisions cited:
T 0164/83, T 0495/91, T 0741/91

.../...

Catchword:
I. The question of inventive step can only be objectively answered if an unrealistic approach is avoided. This implies that it is not appropriate to formulate an artificial and unrealistic technical problem which a skilled person, in practice, would not have considered (following T 495/91 and T 741/91). Therefore, a document that has been disregarded by those skilled in the art for more than 20 years and which has never been used during this period as a basis for further development, and which, moreover, is completely silent about the extent of the promised activity, which document, finally, does not even mention, let alone discuss, the relevant state of the art, so that the person skilled in the art is not in the position to recognise any technical advantage of these compounds in respect of that state of the art, does not represent the closest state of the artand cannot, therefore, be used for defining a realistic technical problem (No. 4.2 of the reasons).

II. It is not permissible to ignore, for the purpose of defining the technical problem, technical evidence establishing technically useful properties of the claimed compounds, including the obtained level of activity (see No. 4.6 of the reasons).

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0334/92 - 3.3.1

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

Appellant: Eisai Co., Ltd.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 23 August 1991 refusing European patent application No. 86 110 080.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

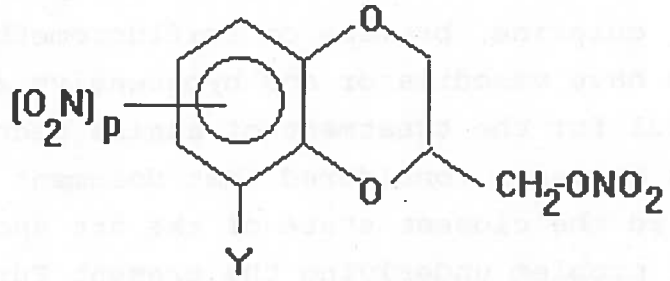
Chairman: A.K.A. Jahn
Members: R.K. Spangenberg
J.A. Stephens-Ofner

Summary of Facts and Submissions

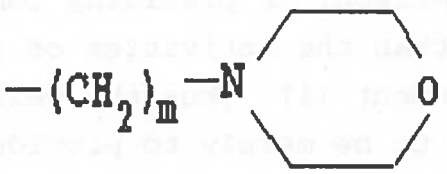
I. This appeal was filed on 23 October 1991 against the decision of the Examining Division of 23 August 1991 refusing European patent application No. 86 110 080.8, filed on 22 July 1986, and published under No. 0 210 581. The appropriate fee was paid on the same date.

II. The decision under appeal was based on two sets of claims, the first set comprising eight claims for the Contracting States other than AT and the second four claims for AT. Claim 1 of the first set read as follows:

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



wherein p stands for an integer of 1 or 2; Y is a group represented by -OR in which R denotes a hydrogen atom, a lower alkyl, a lower alkoxycarbonyl, an alkanoyl, nicotinoyl or a group represented by the formula

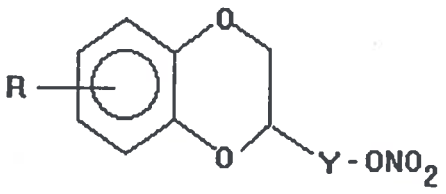


in which m is 1 or 2; or a pharmacologically acceptable salt thereof."

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, which compounds have vasodilator and hypotensive activity and were useful for the treatment of angina pectoris. The Examining Division considered that document (1) represented the closest state of the art and that the technical problem underlying the present European patent application 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). Thus the relevant technical problem was held to be merely to provide compounds of a chemical structure and a therapeutical 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 nitratoalkyl group, including those proposed in the present European patent application, would have such a similar activity.

III. A Statement of Grounds of Appeal was received on 20 December 1991. On 4 March 1994, after a telephone conversation with the Rapporteur of the Board of Appeal, concerning some possible objections against the above sets of claims, the Appellant (the Applicant) filed two fresh sets of claims, comprising eight claims for the Contracting States except AT and four claims for AT. In Claim 1 of the first set the expression "alkanoyl" in Claim 1 underlying the decision under appeal was replaced by "alkanoyl group derived from aliphatic monocarboxylic acids having 1 to 6 carbon atoms".

The Appellant submitted that the approach of the Examining Division to assess inventive step, namely a direct comparison of the therapeutic activities of the claimed compounds and the prior art compounds having the greatest structural similarity, was not the only one possible. Consequently, even if on this approach an inventive step could not be established, this would not mean that the claimed compounds were obvious, since the presence of an inventive step could follow from other considerations. Thus he submitted that the compounds he had used for comparison were the ones that were and still are commonly used in therapy, and that it would be more reasonable and logical to compare his newly developed compounds with those compounds of the state of the art, rather than with compounds which, although having greater structural similarity, were, in the absence of any quantitative assessment of their

activity, of unknown therapeutic significance and were not readily comparable with the new compounds.

In addition, he submitted that the claimed compounds showed important structural differences when compared with those disclosed in document (1), and that no person skilled in the art would thus have been able to predict the improved pharmacological properties which were shown in the present patent application.

IV. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the sets of claims filed on 4 March 1994.

Reasons for the Decision

1. The appeal is admissible.

2. The Board is satisfied that no objection under Article 123(2) arises against the subject-matter of these claims (see Claims 1 to 5, 7, 13 to 18 as filed together with the description as filed page 2, lines 13 to 19).

3. The claimed compounds are novel with respect to the content of document (1) (see point II above).

4. *Inventive Step*

4.1 On page 3, lines 8 to 14 of the description of the present patent application, it is stated that two nitrate esters were widely used in the therapeutic treatment of angina pectoris, namely NG, which had been used for more than 100 years and was still considered to be one of the most effective compounds, and the more

recently developed ISDN. On page 4, lines 1 to 9 it is further stated that the present patent application aimed at the development of structurally different nitro-containing compounds having activities stronger than those of these conventional medicines. The description as filed further contained a number of pharmacological test results (pages 10 to 17) demonstrating that one of the claimed compounds, namely 8-hydroxy-2-nitratomethyl-7-nitro-1,4-benzodioxane, has indeed a higher activity and at the same time a lower acute toxicity than NG and ISDN.

However, the Examining Division did not accept these test results as a basis for assessing the inventive step in the present case. Instead, they relied upon document (1), which disclosed chemical compounds which were structurally more closely related to the claimed ones and were also said to have activity against angina pectoris. They stated that the presence of an inventive step could only be acknowledged if an increased activity of the claimed compounds compared with those described in document (1) could be demonstrated. In the absence of any evidence on this point they concluded that the claimed compounds were no more than obvious modifications of the latter compounds.

4.2 The Board cannot accept the validity of this approach. The question of inventive step can only be objectively answered if an artificial, mechanistic and therefore unrealistic approach is avoided. This implies that it is not appropriate to formulate an artificial and unrealistic technical problem which a skilled person, in practice, would not have considered (see also T 495/91 of 20 July 1993, point 4.2 of the reasons and T 741/91 of 22 September 1993, point 3.3 of the reasons). It is thus necessary, after having determined the relevant state of the art in respect of chemical structure and

technically useful properties, to consider carefully whether or not in the specific circumstances of the case, taking into account all available information about the technical context of the claimed invention, a person skilled in the art would in fact have had any, let alone any good reason to select this piece of prior art as the basis for further development.

4.3 In the present case, the Appellant has strongly emphasised that document (1), which was published in 1964, has never been and would never have been considered, let alone seriously considered, by those skilled in the art. This submission is in agreement with the fact that a number of textbooks concerning pharmaceutical chemistry, which have been consulted by the Board, *inter alia* "Burgers Medicinal Chemistry", fourth edition, Part III (1981), pages 94 to 96, and "E. Mutschler, Arzneimittelwirkungen" (1991), pages 417 to 420, do not even mention these compounds among the useful medicaments for the treatment of angina pectoris. Thus the Board accepts the Appellant's assertion that document (1) was disregarded by those skilled in the art for more than 20 years, and, in particular, that no attempt has been made during this long period to take these compounds as a basis for further development. It is also significant that this document is completely silent about the extent of the indicated therapeutic activity. Nor does it mention, let alone discuss, the state of the art relevant at the time, which comprised NG as a medicament of recognised value, so that the person skilled in the art would not have been in the position to recognise any technical advantage of these compounds in respect of the relevant state of the art at the time.

Thus, although it is clear that the Examining Division has correctly identified document (1) as the one describing compounds of the same activity (see page 2, lines 13 to 16) and having the greatest structural similarity to the claimed compounds, the Board nevertheless holds that it is not appropriate to consider document (1) as the closest state of the art and, therefore, as a realistic starting point for the determination of the relevant technical problem, because in the particular circumstances of this case it would be wholly unrealistic to assume that a person skilled in the art would have set out to modify an old class of chemical compounds whose contribution to the technical field was totally unknown, with a view to obtaining new compounds having higher activity than the standard compounds accepted and used, namely NG and ISDN. Thus in the present case an objective assessment of **all** relevant circumstances leads to the conclusion that document (1), in spite of its closest structural similarity and in spite of its identical type of activity to that of the claimed ones cannot be regarded as the appropriate starting point for the assessment of inventive step. In contrast to the Appellant's submission, however, the Board observes that the absence of quantitative test results alone would not have been sufficient to disqualify document (1) in this respect.

Moreover, the compounds of the present amended Claim 1 are esters of nitric acid and glycerol, and are therefore also structurally related to NG.

For these reasons the Board holds that in the present case the closest state of the art for the assessment of inventive step is represented by NG and ISDN, the standard medicaments for treating *angina pectoris* at the priority date of the present patent application, and that the technical problem underlying this patent

application should be seen in providing further chemical compounds which have an improved activity in the treatment of angina pectoris when compared with these known compounds, and are at the same time less toxic.

4.4 It can be seen from Pharmacological Experiments 1 and 2 (pages 10 to 14 of the description as filed) as well as from the toxicity data on page 16 of the description that one of the claimed compounds, namely 8-hydroxy-2-nitratomethyl-7-nitro-1,4-benzodioxane, solves the above-defined technical problem. The Board is satisfied that the above compound is representative of the relatively small group of compounds now claimed and that, therefore, all compounds encompassed by this group solve this problem to about the same extent.

4.5 As already mentioned, document (1) is silent on the extent of the promised activity and does not therefore provide any incentive to modify the compounds it describes. Nor does it suggest the direction of modification, chosen in the present application, in order to obtain compounds which have a superior activity and a lower toxicity than NG or ISDN and are therefore suitable for solving the present technical problem. The other prior art compounds mentioned in the description and in the cited textbooks are not derived from glycerol or 1,4-benzodioxane. The knowledge of their structure and activity therefore does not suggest the structural modifications leading to the compounds now claimed either. The presence of an inventive step can therefore be acknowledged.

4.6 Nor would the result be any different if one would, incorrectly, consider document (1) as the relevant closest state of the art. Even if one would further accept that some activity against angina pectoris may be expected to exist in all compounds having a nitrate

ester group in the molecule, as stated by the Examining Division, it is clear from the test results included in the application as filed that the technical problem solved by the present application was to provide novel compounds not having just **some** activity, but compounds having an activity **higher than that of NG or ISDN**. In the Board's judgment, it is not permissible to ignore, for the purpose of defining the technical problem, any technical evidence establishing technically useful properties of the claimed compounds, including the obtained level of activity.

Document (1) does not contain even the slightest indication as to how to modify the chemical structure of the compounds it describes in order to obtain the high level of activity required for the solution of the above technical problem. According to the present amended Claim 1 the claimed compounds must contain at least one aromatic nitro group and an OR group in position 8 of the benzodioxane ring system, structural elements which are not comprised by the general formula of document (1) (see point II above). Thus this document could not suggest these structural modifications as a solution to the above technical problem. It is therefore not necessary in the present case to rely on a direct comparison with a compound described in document (1).

5. Since the Examining Division had relied in its decision on the earlier appeal decision T 164/83 (OJ EPO 1987, 149), without, however, considering the particular facts upon which that decision was based, the Board wishes to observe that the determination of the appropriate starting point for the formulation of the technical problem depends on the facts of each individual case. In the case decided in T 164/83 the claimed subject-matter overlapped with that of the document which was found to be representative for the closest state of the art, and

in respect of the activity of the claimed compounds falling within that overlapping area it was found, in the absence of any evidence to the contrary, that a person skilled in the art would expect it to be quantitatively comparable with that of the prior art compounds (see No. 6 of the Reasons).

By contrast, in the present case the claimed compounds are structurally well distinguished from those described in document (1), as set out in paragraph 4.6 above. Therefore, the conclusion drawn from the different facts of the case decided in T 164/83, namely that technical progress shown in comparison with marketed products as an alleged support, cannot be a substitute for the demonstration of inventive step with regard to the relevant closest state of the art (see No. 8 of the Reasons, last paragraph), cannot be relevant to the present case, where the marketed products are also the structurally most closely related products which can realistically be taken as the basis for the assessment of the inventive step.

In conclusion, the Board wishes to observe that the circumstances which had to be taken into account in the present case, in particular the age and the insufficient content of document (1), were rather exceptional and that the direct comparison of a claimed compound with the structurally most closely related compound of the state of the art remains normally the most straightforward, and very often the sole, method of deciding the issue of inventive step.

6. For the above reasons the Board holds that the group of compounds according to Claim 1 of the first set meets the requirements of the EPC. Claims 3 and 4 of this set, relating to processes for preparing these compounds, as well as Claims 5 and 8, relating to pharmaceutical

compositions containing them and to the use of these compounds in the preparation of pharmaceutical compositions, define the same invention as Claim 1 in different patent categories. Claims 2, 6 and 7 relate to specific embodiments of this invention. Claims 1, 2 and 4 of the second set (for AT) correspond to Claims 3, 4 and 8 of the first set. Claim 3 of this set relates to the preparation of the compound of Claim 2 of the first set. These claims are therefore likewise allowable.

However, the description is not yet adapted to the present set of claims. Thus not all requirements of the EPC are met by the present application documents. The Board therefore uses its power under Article 111(1) EPC and remits the case to the Examining Division for proper adaptation of the description.

Order

For these reasons it is decided that

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant a patent with the two sets of claims submitted on 4 March 1994, after appropriate adaptation of the description.

The Registrar: The Chairman:

E. Görgmaier A. Jahn