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D E C I S I O N
of 4 November 1999

Case Number: T 0467/94 - 3.3.1

Application Number: 89905764.0

Publication Number: 0374261

IPC: C07D 513/14

Language of the proceedings: EN

Title of invention:
Pyridinium salt and pharmacological composition containing the same

Applicant:
Eisai Co., Ltd.

Opponent:
-

Headword:
Pyridinium compounds/EISAI

Relevant legal provisions:
EPC Art. 56, 111(1)

Keyword:
"Inventive step (yes) - bioisosterism - no pointer to the claimed compounds"
"Remittal"

Decisions cited:
T 0164/83, T 0643/96

Catchword:

-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0467/94 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 4 November 1999

Appellant: Eisai Co., Ltd.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 31 March 1994 refusing European patent application No. 89 905 764.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: J. M. Jonk
S. C. Perryman

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division refusing European patent application No. 89 905 764.0, published as WO 89/10927, and relating to "Pyridinium salt and pharmacological composition containing the same".

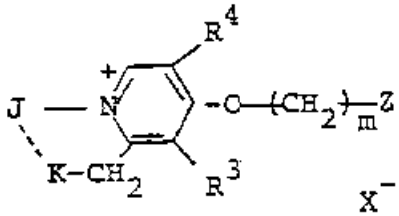
II. The Examining division held that the subject-matter of the set of Claims 1 to 4 submitted on 19 November 1993 lacked inventive step in view of documents

(2) EP-A-0 214 479, and

(4) EP-A-0 171 372.

III. Claims 1, 2 and 3 of said set of claims read as follows:

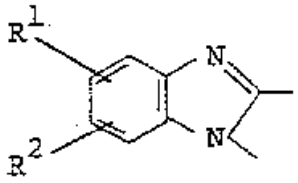
"1. A pyridinium salt having the formula (I):



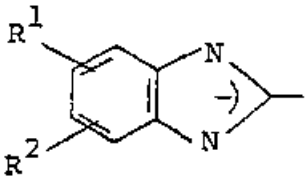
(I)

in which R^3 is a methyl group; R^4 is a hydrogen atom; m is an integer of 3; Z is $-OR^5$; R^5 is a methyl group; X is a pharmacologically acceptable anion; K is (1)-S- or (2)-S-S-R-; R is a straight-chain or branched alkyl group having 1-6 carbon atoms; J is a benzimidazole ring which may have a substituent (S); --- shows a bond

thereby to connect with the nitrogen of the benzimidazole or no bond, provided that (1) when K is -S-, J is a group having the formula:

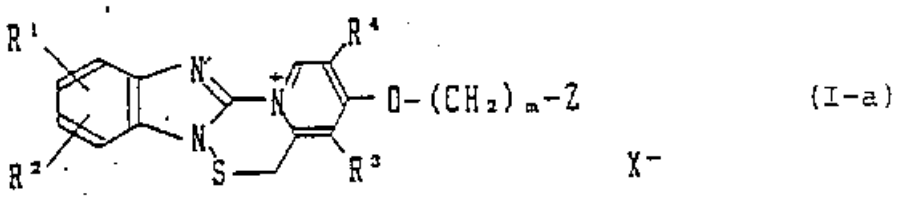


in which R^1 and R^2 each are hydrogen, a straight-chain or branched alkyl group having 1-6 carbon atoms, an alkoxy group derived from straight-chain or branched alkyl group having 1-6 carbon atoms, a halogenated straight-chain or branched alkyl group having 1-6 carbon atoms, an alkoxy carbonyl group derived from straight-chain or branched alkyl group having 1-6 carbon atoms, carboxyl or halogen, (2) when K is -S-S-R, J is a group having the formula:



and X does not exist."

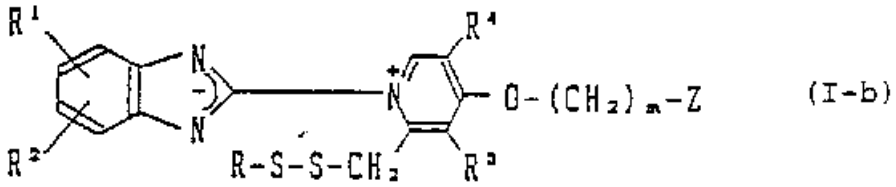
"2. A pyridinium salt as claimed in Claim 1, which is a sulphenamide derivative having the formula (I-a):



(I-a)

wherein R^1 to R^4, m, Z and X are as defined in Claim 1."

"3. A pyridinium salt as claimed in Claim 1, having the formula (I-b):



(I-b)

wherein R, R^1 to R^4, m, Z and X are as defined in Claim 1."

IV. The Examining Division held in particular that a person skilled in the art, faced with the problem of finding further compounds which are useful in the treatment and prevention of human and animal peptic ulcers because of their inhibiting effect on gastric acid secretion, would have expected that this problem could be solved by replacing the alkoxy group at the 4-position of the

pyridinium ring of the prior art compounds by a $-O-(CH_2)_m-Z$ group as defined in the claims of the application in suit, i.e. by a methoxypropoxy ($-O-C_3H_6-OCH_3$) group. In this context, they noted that the prior art compounds, which were not substituted at said position, showed about the same activity as the corresponding alkoxy substituted compounds, and that within the concept of modern bioisosterism an -O- atom and a $-CH_2-$ group were classical isosters, so that the replacement of an alkoxy group by methoxypropoxy could not be considered as a substantial structural modification.

V. The Appellant argued that said replacement of the alkoxy group by the methoxypropoxy group did not represent a minor structural modification and that in the field of pharmaceuticals even small variations in the structure of molecules could result in dramatic changes of their pharmaceutical behaviour. He concluded that for these reasons it was not predictable and therefore not obvious to a skilled person that the compounds of present Claim 1 of the application in suit showed the found activity.

VI. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the documents submitted on 19 November 1993.

VII. Oral proceedings before this Board were held on 4 November 1999. However, after having informed the Board accordingly, the Appellant did not attend this hearing.

VIII. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

2. Present Claim 1 is supported by Claim 1 in combination with Claim 7 (concerning the meaning of R^3, R^4, Z and R^5) and page 5, second paragraph to page 6, first paragraph (concerning the meaning of R, R^1 and R^2) of the application as filed.

   Present Claims 2 and 3 are supported by the Claims 2 and 3 of the application as filed.

   Present Claim 4 corresponds to Claim 8 as filed.

   Thus, all claims of the present set of claims meet the requirement of Article 123(2) EPC.

3. After examination of the citations on file, the Board has reached the conclusion that the subject-matter as defined in all claims is novel. Since this issue was not in dispute, it is not necessary to give reasons for this finding.

4. The remaining issue to be dealt with is whether the subject-matter of the present claims involves an inventive step.

4.1 Article 56 EPC sets forth that an invention involves an inventive step if, having regard to the state of the art (in the sense of Article 54(2) EPC), it is not obvious to a person skilled in the art.

4.2 For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which consists essentially in (a) identifying the closest prior art, (b) assessing the technical results (or effects) achieved by the claimed invention when compared with the closest state of the art established, (c) defining the technical problem to be solved as the object of the invention to achieve these results, and (d) examining whether or not a skilled person starting from the closest prior art **would** arrive at something falling within Claim 1 by following the suggestions made in the prior art in the sense of Article 54(2) EPC.

If the technical results of the invention provide some improvement over the closest prior art, the problem can be seen as providing such improvement, provided this improvement necessarily results from the claimed features for all that is claimed. If, however, there is no improvement, but the means of implementation are different, the technical problem can be defined as the provision of an alternative to the closest prior art.

4.3 In the present case, the Board considers - in agreement with the Examining Division and the Appellant - that the **closest state of the art** is **document (4)** as far as compounds having the **formula (I-a)** as defined in present **Claim 2** are concerned, and by **document (2)** as far as compounds having the **formula (I-b)** as defined in present **Claim 3** are concerned.

Both documents relate to compounds useful as anti-ulcer agents due to their gastric acid secretion-inhibiting activity (see document (4), page 5, third paragraph,

and document (2), second and third paragraph) differing from the compounds of the patent application in suit in that they comprise at the 4-position of the pyridinium ring an alkoxy group having 1-7 carbon atoms (see document (2), page 1, line 30, and document (4), page 4, second paragraph) instead of the group $-O-(CH_2)_m-Z$ as defined in the present claims, i.e. the methoxypropoxy group.

4.4 With respect to this closest prior art, the Appellant contended that he did not have at his disposal evidence showing that the compounds of the application in suit had improved properties. Moreover, he submitted that the provision of such evidence was not necessary in view of the test-reports described in the application in suit, in which compounds of the application in suit were compared with a control compound (Omeprazole).

4.5 In these circumstances, and in view of the established jurisprudence of the Boards of Appeal holding that technical progress shown in comparison with a commercial product could not be a substitute for the demonstration of inventive step with regard to the closest prior art (see e.g. T 164/83, OJ EPO 1987, 149), it is the Board's position that in the light of the closest prior art represented by documents (2) and (4) the technical problem underlying the application in suit can be seen in the provision of further useful anti-ulcer agents.

4.6 The present patent application suggests, as the solution to this problem, the provision of the group of compounds as defined in present Claim 1. This group of compounds has been divided in two subgroups as defined

in Claims 2 and 3 having the formulas (I-a) and (I-b) respectively.

4.7 Having regard to the pharmacological test-examples described in the application in suit using the compound of Example 1 falling under the scope of formula (I-a) as defined in present Claim 2 (see page 13, second paragraph to page 14, penultimate paragraph, of the application as filed), and the compound of Example 12 falling under the scope of formula (I-b) as defined in present Claim 3 (see page 26, last paragraph to page 28, second paragraph, of the application as filed) showing that these compounds have an excellent effect of inhibiting acid secretion based on intense H^+-K^+ATPase inhibition effect, the Board considers it plausible that the technical problem as defined above has been solved.

4.8 The question now is whether the cited documents would have suggested to a person skilled in the art solving the above-indicated technical problem in the proposed way.

4.9 Documents (2) and (4) disclose - as indicated above under point 4.3 - compounds useful as anti-ulcer agents due to their gastric acid secretion-inhibiting activity. These prior art compounds differ from those of the patent application in suit in that they comprise at the 4-position of the pyridinium ring *inter alia* an alkoxy group having 1-7 carbon atoms. Therefore, in the Board's judgment, these documents do not give any pointer to the skilled person that the technical problem underlying the present patent application as defined above could be solved in accordance with

present Claim 1, i.e. by replacing said alkoxy group by the methoxypropoxy group.

4.10 In this context, the Examining Division held in their decision that the replacement of the alkoxy group by the methoxypropoxy group would have been obvious in the light of the concept of modern bioisosterism considering that an -O- atom and a $-CH_2-$ group were classical isosters.

However, in the Board's judgment, when deciding upon inventive step in relation to pharmacologically active compounds it is not essential whether a particular substructure of a compound could be replaced by another known isosteric one, but whether information was available on the impact of such a replacement on the pharmacological activity of the specific group of compounds concerned (see also e.g. the unpublished decision T 643/96 dated 14 October 1996).

In the present case, the Examining Division did not provide any evidence that the replacement a $-CH_2-$ subgroup in said alkoxy substituent of the group of compounds defined in documents (2) and (4) by an -O- atom would have no substantial influence on their pharmacological properties. Moreover, documents (2) and (4) - as indicated above - unambiguously disclose that at the 4-position of the pyridinium ring only particular substituents are suitable, so that the skilled person would have expected that this is an essential requirement for having the desired anti-ulcer properties.

Therefore, the Examining Division's point of view in

this respect cannot be accepted by the Board.

4.11 In conclusion, the Board finds that the subject-matter of Claims 1, 2 and 3 involve an inventive step in the sense of Article 56 EPC.

Claim 4, which relates to pharmaceutical compositions comprising a compound as defined in Claims 1 to 3, derives its patentability from that of these preceding claims.

5. Despite the fact that the Appellant's appeal was successful, the application in suit still needs amendments to meet the requirements of Article 84 EPC since present Claim 1 contains an unclear definition of the group of compounds by referring to a formula (I) comprising a number of variants, namely R^3, R^4, m, Z and R^5, which are actually no variants at all, but each time only represent one specific meaning, namely methyl, hydrogen, the value 3, the group $-OR^5$, and methyl as the meaning of said R^5, respectively, as well as two provisos with respect to the symbols J and K in order to define the two subgroups having the formulas (I-a) and (I-b) specified in present Claims 2 and 3 respectively. In this context, the Board notes that the required clarity and conciseness could be met, for instance, by replacing present Claims 1, 2 and 3 by an amended Claim 1 in which the claimed compounds are defined by indicating that they have the formula (I-a) or the formula (I-b), in which formulas R^3 and R^4 are replaced by CH_3 and H respectively, the group $-O-(CH_2)_m-Z$ is replaced by $-O-(CH_2)_3-OCH_3$, and the remaining substituents R^1 and R^2 are as defined in present Claim 1.

In these circumstances, and having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance, the Board makes use of its competence under Article 111(1) EPC and remits the case to the first instance for further prosecution in this respect.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance for further prosecution.

The Registrar: The Chairman:

E. Görgmaier A. Nuss