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D E C I S I O N
of 30 March 1998

Case Number: T 0156/95 - 3.3.1

Application Number: 91108348.3

Publication Number: 0458331

IPC: C07D 498/14

Language of the proceedings: EN

Title of invention:
Pyrido[3,4-b]pyrrolo[1,2-e][1,4,5]oxadiazepines and related
analogs, a process for their preparation and their use as
medicaments

Applicant:
Hoechst Marion Roussel, Inc.

Opponent:
-

Headword:
Pyrido-pyrrolo-oxadiazepines/HOECHST MARION ROUSSEL

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (yes) - chemical compounds - non obvious
alternative"
"Bioisosterism"

Decisions cited:
T 0643/96

Catchword:
-



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30

Case Number: T 0156/95 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 30 March 1998

Appellant: Hoechst Marion Roussel, Inc.
Kansas City, Missouri 64137-1405 (US)

Representative: Losert, Wolfgang Dr.
Hoechst AG
Patent- und Lizenzabteilung
Gebäude K 801
65926 Frankfurt am Main (DE)

Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 19 September 1994
refusing European patent application
No. 91 108 348.3 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. J. Nuss
Members: P. Krasa
R. E. Teschemacher

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division refusing European patent application No. 91 108 348.3 (publication No. 0 458 331) and relating to pyrido[3,4-b]pyrrolo[1,2-e][1,4,5]oxadiazepines and related analogs, a process for their preparation and their use as medicaments.

II. In the decision under appeal, the Examining Division argued that they could not accept the Appellant's arguments regarding the lack of usefulness of the concept of "bioisosterism" for predicting the pharmacological properties of novel chemical compounds, and refused the application, without defining a technical problem and applying the said concept, on the grounds that the subject-matter of Claim 1 was obvious over documents

- (1) EP-A-0 144 729, and
- (5) Burger, "Medicinal Chemistry", Part I, 3rd Ed., Wiley-Interscience, 1970.

The Board will also refer to documents

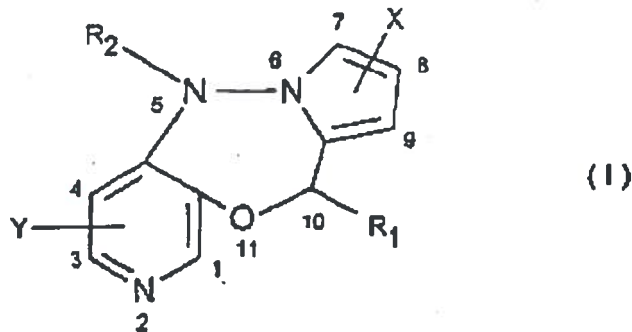
- (2) EP-A-0 300 356,
- (3) US-A-4 029 672 and
- (4) DE-A-2 708 110.

III. The Appellant, in his statement of grounds for appeal, submitted in essence that the compounds of the application in suit differed structurally from those disclosed in documents (1) and (2) by the replacement of two carbon atoms by two nitrogen atoms. Further, he

submitted that a person skilled in the art would not have replaced a =C- group by a =N- group in an analgesic, since it was known that such a replacement resulted in a decrease in analgesic activity.

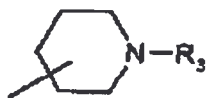
IV. Responding to a communication from the Rapporteur indicating several deficiencies in the claims as submitted by the Appellant together with the statement of grounds for appeal, the Appellant submitted on 24 February 1998 a set of Claims 1 to 8 for all designated states except Spain and Greece, Claim 1 of which reads:

"A compound of the formula I



where

- X is hydrogen, halogen or (C₁-C₆)alkyl;
 Y is hydrogen, halogen, (C₁-C₆)alkyl, or trifluoromethyl;
 R₁ is hydrogen, (C₁-C₆)alkyl, di(C₁-C₆)alkylamino(C₁-C₆)alkyl or



R₃ being hydrogen or (C₁-C₆)alkyl;

R₂ is hydrogen or (C₁-C₆)alkyl;
or a pharmaceutically acceptable acid addition salt
thereof."

He further submitted Claims 1 to 6 for Spain and Greece, together with amended pages 1, 2, and 9 of the description, and requested that the decision under appeal be set aside and a patent be granted on the application in suit on the basis of these claims. The Appellant also requested oral proceedings, in case the Board were to raise further objections.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

Amended Claim 1 for all the designated contracting states except Spain and Greece differs from Claim 1 as originally filed by the deletion of originally specified alternatives from the definitions of the residues designated with Y, R₁, and R₂, and by the substitution of "(C₁-C₆)" for "lower", which replacement finds its basis in the second paragraph on page 2 of the application as originally filed. Apart from the replacement of "lower" by "(C₁-C₆)", Claims 2 to 8 for all the designated contracting states except Spain and Greece have the same wording as the respective original Claims 2 to 8. Therefore, Claims 1 to 8 for all the designated contracting states except Spain and Greece comply with the requirements of Article 123(2) EPC, as do Claims 1 to 6 for Spain and Greece, for which the above considerations apply *mutatis mutandis*.

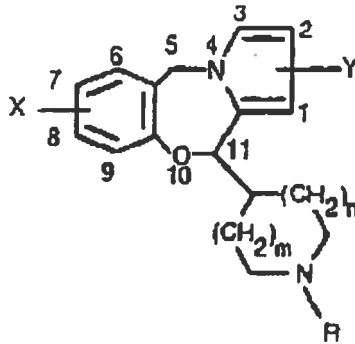
3. *Novelty*

The subject-matter of the claims is not disclosed in any of the citations on file and is therefore novel. Since this is not in dispute, no further comments from the Board are necessary on this issue.

4. *Inventive Step*

- 4.1 The Examining Division considered document (1) to represent the most relevant state of the art. The Board has no reason to disagree and accepts this citation as the starting point for the evaluation of inventive step.

Document (1) discloses that substituted pyrrolo-benzoxazepines of the general formula



are useful as analgesic agents and also as antipsychotic agents (page 1, formula I, in combination with page 17, lines 13 to 14, and page 13, lines 16 and 17; for the purpose of this decision it is not necessary to give the definitions of X, Y, R, m, and n).

It follows that the technical problem to be solved can be seen in providing further chemical compounds useful as analgesic agents.

In view of the inhibition of phenylquinone-induced writhing in mice, reported for two representatives of the claimed group of compounds (Table 1 on page 6 of the application in suit both as originally filed and as published), the Board is satisfied that the subject-matter of Claim 1 solves the said technical problem.

4.2 It remains to be decided whether or not the compounds of Claim 1 of the application in suit meet the requirement of inventive step.

4.2.1 The group of compounds generically disclosed in document (1) and also in documents (2), (3), and (4) are all **benzoxazepine derivatives**. In the decision under appeal, the Examining Division argued that the replacement of two C-atoms of the compounds of document (1) by two N-atoms, resulting in the compounds of the present Claim 1, was obvious in view of the concept of bioisosterism (see the appealed decision, the paragraph bridging pages 2 and 3, and the last paragraph on page 5). This concept belongs to the common general knowledge of those skilled in the art and may provide some general guidance for rationally developing a research program in a particular pharmacological field (as already mentioned by the Appellant to the Examining Division). However, it has to be applied with caution as soon as it comes to reliably predicting the pharmacological properties of novel chemical compounds, since it is not a law of nature of general validity but rather an **empirical rule**, which in each particular case needs to be experimentally verified in order to establish whether or not it fits. It could only provide a pointer to the claimed solution of the existing technical problem if

there was an **established** case of bioisosterism for the particular class of chemical compounds concerned. The Board accepts that =N- and =C- are well known isosteric groups. However, when deciding on inventive step in relation to pharmacologically active compounds, what is essential is not whether a particular sub-structure of a chemical compound is replaced by another known isosteric one, but whether information was available on the impact of such a replacement on the pharmacological activity profile of the (group of) specific compound(s) concerned (see T 0643/96 of 14 October 1996, in particular Reasons 4.2.3.3 and 4.2.3.5, not published in the OJ EPO).

- 4.2.2 Under the prevailing circumstances of this case, the Examining Division's recourse to the concept of bioisosterism was not justified, since no information (apart from that of the application in suit) was available to them for assessing whether or not this concept could be verified in the field of benzoxazepine analgesics.
- 4.2.3 The Board has, of its own motion, also considered documents (2), (3), and (4) disclosing analgesics, all comprising the benzoxazepine substructure as a mandatory technical feature.

Thus, in the Board's judgement, a skilled person would have assumed that this structural feature is a mandatory requirement for maintaining the desired analgesic property of the compounds concerned. In the absence of further information, he would not have had any reason to expect that a replacement of a C-atom by the isosteric N-atom, let alone of two C-atoms by two N-atoms (as in the compounds of present Claim 1), would result in compounds retaining the desired analgetic activity.

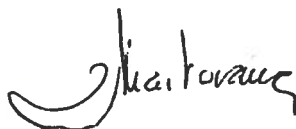
4.3 It follows from the above that the subject-matter of Claim 1 for the designated contracting states except Spain and Greece is not rendered obvious by documents (1) to (5), either alone or in combination. Dependent Claims 2 to 5 relating to specific embodiments of this invention, Claim 6 relating to pharmaceutical compositions comprising them, Claim 7 directed to the use of a compound of Claim 1 for the preparation of a medicament having analgesic activity, and Claim 8 relating to a process for the preparation of the compounds of Claim 1 are based on the same inventive concept and derive their patentability from that of Claim 1, as do Claims 1 to 6 for Spain and Greece.

5. In view of the above, it was not necessary to schedule oral proceedings.

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 on the basis of the following documents:
 - Claims 1 to 8 for all the designated contracting states except Spain and Greece, as filed on 24 February 1998;
 - Claims 1 to 6 for Spain and Greece, as filed on 24 February 1998;
 - pages 3 to 8 and 10 to 14 of the description as originally filed; and
 - pages 1, 2 and 9 of the description as filed on 24 February 1998.

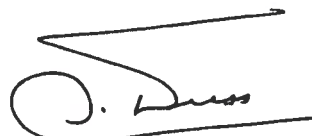
The Registrar:



P. Martorana



The Chairman:



A. Nuss