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D E C I S I O N
of 25 April 2001

Case Number: T 0821/96 - 3.3.1

Application Number: 91917994.5

Publication Number: 0506905

IPC: C07D 213/56

Language of the proceedings: EN

Title of invention:
Piperazine Derivatives

Applicant:
JOHN WYETH & BROTHER LIMITED

Opponent:
-

Headword:
Piperazines/WYETH & BROTHER

Relevant legal provisions:
EPC Art. 56, 84, 111, 113
EPC R. 67

Keyword:
"Clarity and support within the meaning of Article 84 EPC (yes, after amendments)"
"Reimbursement of the appeal fee (no) - outcome of the decision not affected - equity within the meaning of Rule 67 EPC (no)"
"Inventive step (yes, afer amendment) - non-obvious improvement"

Decisions cited:
T 0682/91, T 0712/97

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0821/96 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 25 April 2001

Appellant: JOHN WYETH & BROTHER LIMITED
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 4 April 1996 refusing European patent application No. 91 917 994.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

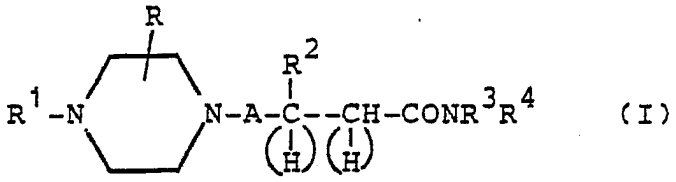
Chairman: A. J. Nuss
Members: J. M. Jonk
C. Rennie-Smith

Summary of Facts and Submissions

I. This appeal lies from the decision of the Examining Division refusing the European patent application No. 91 917 994.5, published under the International Publication Number WO 92/06960, and relating to piperazine derivatives.

II. The decision was based on Claims 1 to 9 of the application as filed, Claim 1 reading as follows:

"A compound of formula



(I)

wherein

A is an alkylene chain of 1 or 2 carbon atoms optionally substituted by one or more lower alkyl groups,

R is hydrogen or lower alkyl,

R^1 is a mono- or bi-cyclic aryl or a heteroaryl radical,

R^2 is an aryl radical, a heteroaryl radical, or an aryl- or heteroaryl-lower alkyl radical,

R^3 is hydrogen, lower alkyl or aryl and R^4 is hydrogen, lower alkyl, cycloalkyl, cycloalkyl(lower)alkyl, aryl, or aryl(lower)alkyl or R^3 and R^4 together with the

nitrogen atom to which they are both attached represent a saturated heterocyclic ring which may contain a further hetero atom and the dotted line represents a single or double bond, the hydrogen atoms shown in brackets being present when the dotted line represents a single bond."

III. The Examining Division held that the subject-matter of Claim 1 was novel, but that it did not meet the requirements of clarity under Article 84 EPC and of inventive step under Article 56 EPC.

Concerning the objection of lack of clarity the Examining Division considered that the term "lower" in the claims concerning the radicals referred to was not sufficiently clear and therefore did not meet the requirements of Article 84 EPC.

Furthermore, it held with respect to the objection of lack of inventive step that the subject-matter of Claim 1 was obvious to the skilled person in view of documents

(A) US-A-4 921 958, and

(B) Ind. Chim. Belge, 28 (1963), 123 to 134.

In this context, the Examining Division considered that the compounds of Claim 1 of the present application differed from those described in document (A) only in that the compounds of the present application contained a methylene group between the terminal amide group and the carbon atom substituted by the aromatic rest as claimed. Moreover, it considered that the technical problem underlying the application in suit in the light

of said document (A) was the provision of further piperazinyl derivatives which could bind 5-HT receptors, but that in the absence of any surprising effect and in view of the broad scope of Claim 1, the solution of this problem by providing the compounds as defined in Claim 1 did not involve an inventive step in view of document (B), since this document disclosed similar piperazine compounds showing neurotropic activity and comprising an alkylene group (Z) between the piperazine group and the terminal amide group (R") which might be varied in length.

IV. Oral proceedings before the Board were held on 25 April 2001.

V. In a communication of 1 March 2001 and during these oral proceedings, the Board indicated its provisional views including:

(a) that the term "lower" in the claims concerning the radicals referred to appeared to lack clarity in view of the Board's decision T 1129/97 of 26 October 2000 (to be published in the OJ EPO) in a comparable case,

(b) that the scope of the originally filed Claim 1 and the main claims of the auxiliary requests 1 and 2 then on file seemed to be too broad in view of the technical information provided in the application in suit from which it appeared that the presence of a hexahydroazepinyl ring as part of the terminal amide group would be an essential feature of the claimed invention, and

(c) that it would be not credible in the light of the

cited prior art documents that all substituents falling under the broad definitions of R^1 and R^2 would give compounds showing the alleged 5-HT_{1A} binding activity.

VI. The Appellant, having regard to the Board's objections, ultimately defended the patentability of the application in suit on the basis of a main request and auxiliary requests 1 to 3 as submitted during the oral proceedings.

Claim 1 of this main request concerned a compound having the formula (I) as indicated in Claim 1 of the application as filed (see point II above), wherein:

"A is CH_2,

R is hydrogen or C_{1-6} alkyl,

R^1 is a mono- or bi-cyclic aryl or a mono or bicyclic nitrogen containing heteroaryl radical,

R^2 is an aryl radical, or a pyridinyl, pyrimidinyl or pyrazinyl radical,

R^3 and R^4 together with the nitrogen atom to which they are both attached represent a hexahydroazepino ring;

and the dotted line represents a single or double bond, the hydrogen atoms shown in brackets being present when the dotted line represents a single bond;

and wherein 'aryl' means an aromatic radical having 6 to 12 carbon atoms and 'heteroaryl' means an aromatic radical containing 5 to 11 ring atoms, the R^1 and R^2

radicals being optionally substituted by one or more substituents selected from C_{1-6} alkoxy, C_{1-6} alkylthio, halogen, trifluoromethyl, nitro, carbalkoxy, carboxamido, cyano, amino, C_{1-6} alkylamino and di(C_{1-6} alkylamino)."

It argued, with respect to the required inventive step, in summary:

(a) that the compounds of present Claim 1 essentially differed from those disclosed in document (A) in that the compounds of the present application contained a specific terminal amide group, namely the group $-CONR^3R^4$ wherein R^3 and R^4 together with the nitrogen atom to which they are both attached represent a hexahydroazepino ring and, in addition, a methylene group between said terminal amide group and the aromatic radical containing carbon atom,

(b) that the presently claimed compounds in comparison with the compounds of document (A) showed an improved 5-HT_{1A} binding activity as well as a more selective binding activity for the 5-HT_{1A} receptor compared to their binding activity for the á$_1$ receptor as supported by the test report submitted on 8 August 1996,

(c) that in view of the teaching of the cited documents (A) and (B) it was in fact not necessary to show an unexpected effect of the claimed compounds, and

(d) that the provision of the compounds defined in present Claim 1 having improved or comparable

binding activity for the 5-HT_{1A} receptor compared to those of document (A) was not obvious to the skilled person, because neither of documents (A) and (B) provided any incentive to insert a methylene group between said terminal amide group and the aromatic radical containing carbon atom, and to replace the terminal amide group of the compounds of document (A) by the group -CO-NR^3R^4 wherein R3 and R4 together with the nitrogen atom represent a hexahydroazepino ring.

Furthermore, it requested the reimbursement of the appeal fee alleging a substantial procedural violation by the Examining Division in that it refused the application in suit without prior warning and based its decision on the ground of lack of clarity under Article 84 EPC on which it had no opportunity to present its comments. In this context, it submitted during the oral proceedings before the Board a copy of the communication of the Examining Division dated 17 July 1995 as received by the Appellant which showed, unlike the copy of the same communication in the Examining Division file, that an objection of lack of clarity was first raised only in the first instance decision.

VII. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or alternatively auxiliary requests 1 to 3 submitted during the oral proceedings; and that the appeal fee be refunded.

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

Reasons for the Decision

1. The appeal is admissible.

2. *Request for reimbursement of the appeal fee*

2.1 According to Rule 67 EPC, reimbursement of the appeal fee shall be ordered where the Board of Appeal deems an appeal to be allowable and if such reimbursement is **equitable** by reason of a **substantial** procedural violation.

2.1 In the present case, the Appellant claimed a substantial procedural violation on two grounds: first, that the Examining Division refused the application in suit without a prior warning and, second, that the decision was based on the ground of lack of clarity under Article 84 EPC on which it had been given no opportunity to comment.

2.2 Concerning the Appellant's first complaint, the Board observes that according to the established case law of the Boards of Appeal, it is left to the Examining Division's discretion to decide whether to issue a further invitation to present comments under Article 96(2) EPC. Moreover, such a further invitation would only be appropriate if it would appear likely that, in the light of the applicant's reply, the examination proceedings would terminate in the granting of a patent.

In the present case, the Examining Division clearly indicated in its first and only communication (which, on this subject, is the same both as received by the

Appellant as on the Examining Division file) that inventive step could only be acknowledged if the Appellant were to provide evidence of an unexpected effect of the claimed compounds, to which the Appellant only replied it was not necessary to submit any such evidence. In these circumstances, the Board cannot see a procedural violation by the Examining Division in not sending a further invitation to file observations.

2.3 With respect to the second complaint, the Board agrees with the Appellant that the Examining Division committed a procedural violation in basing its decision on the ground of lack of clarity under Article 84 EPC on which the Appellant had been given no opportunity to comment. This arose from the fact that the communication of 17 July 1995 received by the Appellant, unlike the EPO dossier copy, did not refer to that objection at all, and the Board considers that sending one version of a communication to a party while placing a different version on the file is also a procedural violation.

However, the existence of a procedural violation is not by itself sufficient for reimbursement. The requirement of Rule 67 EPC is - as indicated above - that the reimbursement must be equitable by reason of a substantial procedural violation.

From the decision under appeal it is clear that the Examining Division held that the subject-matter of the claims then on file did not involve an inventive step. The Appellant was thus obliged to appeal to overcome this objection as to which there was no procedural violation. Therefore, although the inclusion in the decision of the ground of lack of clarity without

giving the Appellant an opportunity to deal with the issue was undoubtedly a violation of the right to be heard under Article 113(1) EPC, the appeal fee would have been payable in any event for reasons unrelated to any such violation. Thereby it would not, in the Board's judgment, be **equitable** to reimburse the appeal fee pursuant to Rule 67 EPC notwithstanding the procedural violation, or indeed two such violations, which occurred in this case (cf. the decisions T 682/91 of 22 September 1992 at point 4.2 and T 712/97 of 27 January 2000 at points 2.7 to 2.11 (both unpublished in OJ EPO)).

3. *Main request*

3.1 Amendments under Article 123(2) EPC

3.1.1 The subject-matter of Claim 1 of this request is supported by the application as filed as follows:

(a) by Claim 1; and

(b) page 4, line 5, concerning the meaning of A;

(c) page 2, lines 9 and 10, concerning the meaning of R, in particular with respect to the claimed C_{1-6} alkyl group;

(d) page 3, lines 9 to 13, concerning the meaning of R^1, in particular with respect to the mono or bicyclic nitrogen containing heteroaryl radical;

(e) page 3, lines 14 to 18, concerning the meaning of R^2, in particular with respect to the specified heteroaryl radicals;

(f) page 4, line 10, and the examples, concerning the $-NR^3R^4$ rest defined as a hexahydroazepino ring; and

(g) page 2, lines 14 to 21, and page 2, last line to page 3, line 13, with respect to the meaning of the expressions "aryl" and "heteroaryl" and concerning the specified optional substituents of R^1 and R^2.

Therefore, the subject-matter of present Claim 1 does not contravene Article 123(2) EPC, which requires that no subject-matter extending beyond the application as filed is added by an amendment to a European patent or patent application.

3.2 Support and clarity under Article 84 EPC

3.2.1 Concerning the question of support under Article 84 EPC, the Board firstly observes that according to the established jurisprudence of the Boards of Appeal, Article 84 EPC has to be interpreted as meaning that a claim has to specify all the essential features which are necessary for solving the technical problem with which the application is concerned. Consequently, all technical features described in the description of an application which are apparently essential to the alleged invention, and in particular such features which distinguish the invention from the closest state of the art, have to be present in the claims.

3.2.2 In the present case, the compounds of the application in suit as presently defined in Claim 1 differ from those of the cited prior art documents (A) and (B) in that the compounds of the application in suit contain as essential features a specific terminal amide group,

namely the group -CONR^{3}R^4 wherein R^3 and R^4 together with the nitrogen atom to which they are both attached represent a hexahydroazepino ring and, in addition, a methylene group between said terminal amide group and the aromatic radical containing carbon atom. Moreover, the scope of Claim 1 has been restricted with respect to the meanings of R^1 and R^2 to preferred embodiments. In these circumstances and in view of the fact that the Appellant should have the benefit of a reasonably broad patent protection, in the Board's judgment, present Claim 1 now meets the requirement of support within the meaning of Article 84 EPC.

3.2.3 Furthermore, in the Board's judgment, present Claim 1 also meets the requirement of clarity within the meaning of Article 84 EPC. Since the Examining Division only based its objection in this respect on the presence in the claims then on file of the term "lower" in combination with the various groups referred to and present Claim 1 no longer includes this term, no further comment is required.

3.3 Inventive step

3.3.1 Article 56 EPC states that an invention is held to involve 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.

3.3.2 In deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which involves essentially

(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 in the light thereof the technical problem which the invention addresses and successfully solves,

(d) verifying that the defined technical problem is solved by the embodiments encompassed within the claimed solution, and

(e) 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.

3.3.3 The Board considers, in agreement with both the Appellant and the Examining Division, that the closest state of the art with respect to the claimed subject-matter of the application in suit is the disclosure of document (A).

This document, like the application in suit, is concerned with piperazine compounds having a serotine 5-HT_{A1} receptor affinity (see column 1, lines 40 to 47). Furthermore, as indicated above, the compounds of this document essentially differ from the compounds presently claimed, firstly, in that the last compounds contain a terminal -$CONR^3R^4$ group, wherein R^3 and R^4 together with the nitrogen atom to which they are both attached represent a hexahydroazepino ring, instead of a -CO-NR^1-adamantyl rest and, secondly, in that they contain a methylene group between said terminal -$CONR^3R^4$ amide group and the aromatic radical containing carbon

atom (see document (A), column 1, line 47 to column 2, line 2).

3.3.4 Regarding this closest state of the art, the Appellant contended by referring to its test-report filed on 8 August 1996 that the compounds of present Claim 1 were not only unexpectedly more potent as 5-HT_{A1} binding agents, but also showed a more selective binding affinity for the 5-HT_{A1} receptor compared to their binding affinity for the $á_1$ receptor. However, in view of the test-results given in the Table of this test-report, and in particular the incorrect selectivity values indicated in the right column of said Table, in the Board's judgment only the improved binding affinity has been sufficiently substantiated.

Thus, in the light of the closest state of the art, the technical problem underlying the application in suit, which is credibly solved, can be seen in the provision of piperazine compounds having an improved 5-HT_{A1} binding affinity.

3.3.5 This technical problem is solved by the provision of the compounds as defined in present Claim 1.

3.3.6 In view of the results described in point 3.3.4 above, the Board also accepts that the stated problem has been succesfully solved within the whole area claimed.

3.3.7 The question now is whether the claimed solution would have been obvious to the skilled person in view of the cited prior art.

3.3.8 As indicated above, document (A) does not point the skilled person to compounds having the characteristic

structural features of the compounds as presently claimed (see point 3.3.3 above). Therefore, this document cannot render the claimed subject-matter obvious by itself.

Furthermore, document (B) relates to piperazine compounds which do not contain the two characteristic structural features of the compounds as presently claimed either (see page 123, right column, last paragraph to page 124, left column, first paragraph). Moreover, although it discloses that the compounds defined therein show a neurotropic activity, it clearly teaches that the compounds having - like the compounds of the present application - a terminal amide group (R") show less activity than those having instead a terminal nitrile group (R") (see page 134, left column, under the third conclusion).

Therefore, in the Board's judgment, documents (A) and (B) do not suggest to the skilled person that the technical problem underlying the application in suit could be solved by providing a compound as now claimed.

3.3.9 Thus, for the above reasons, the Board concludes that the subject-matter of present Claim 1 involves an inventive step under Article 56 EPC.

4. *Auxiliary requests*

4.1 In the light of the above findings, it is not necessary to consider the Appellant's auxiliary requests.

5. *Remittal to the first instance*

5.1 Although the Board has come to the conclusion that the

subject-matter of Claim 1 of the present main request meets the requirements of Article 84 EPC and involves an inventive step under Article 56 EPC, the present application still needs further examination in order to establish whether the further claims and the description fulfil the requirements of the EPC.

However, the function of the Boards of Appeal being primarily to give a judicial decision on the correctness or otherwise of first instance decisions, the Board (pursuant to its discretion under Article 111(1) EPC) remits the case to the Examining Division for further prosecution on the basis of the claims of the present main request. This will not prevent the Appellant making further amendments to these claims as necessary.

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 on the basis of the main request.

3. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

N. Maslin A. Nuss