BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 20 November 2000

Case Number: T 1101/98 - 3.3.4

Application Number: 93304497.6

Publication Number: 0574256

IPC: C07H 9/04

Language of the proceedings: EN

Title of invention:
Imidate derivatives of pharmaceutically useful anticonvulsant sulfamates

Applicant:
MCNEILAB, INC.

Opponent:
-

Headword:
Anticonvulsants/MCNEILAB, INC.

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step - (no)"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1101/98 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 20 November 2000

Appellant: MCNEILAB, INC.
Welsh and McKean Roads
Spring House
Pennsylvania 19477-0776 (US)

Representative: Mercer, Christopher Paul
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 18 June 1998 refusing European patent application No. 93 304 497.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

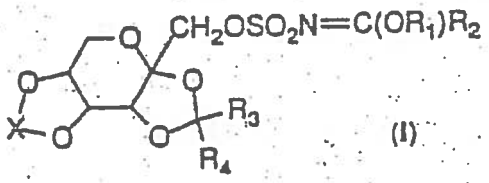
Chairwoman: U. M. Kinkeldey
Members: F. L. Davison-Brunel
C. Holtz

Summary of Facts and Submissions

I. The appeal lies from the decision of the Examining Division dated 18 June 1998 to refuse the European patent application for lack of inventive step of the subject-matter of claim 1.

Claim 1 read as follows:

"1. A compound of the formula (I):



wherein R_1 is selected from any of C_1-C_{10} alkyl or C_3-C_{10} cycloalkyl;
wherein R_2 is selected from any of H, C_1-C_{10} alkyl, C_1-C_6 alkoxy, C_3-C_{10} cycloalkyl, or phenyl;
wherein R_3 and R_4 are the same or different and are selected from any of H, C_1-C_6 alkyl, or are taken together to form a cyclopentyl or cyclohexyl ring;
wherein X is CR_5R_6 wherein R_5 and R_6 are the same or different and are selected from any of H, C_1-C_6 alkyl, C_1-C_4 perfluoroalkyl, or are taken together to form a cyclopentyl or cyclohexyl ring, or X is $S(R_7)_n(R_8)_p$, wherein R_7 and R_8 are the same or different and are selected from either oxygen or NR_9, where R_9 is selected from any of hydrogen, C_1-C_4 alkyl, C_1-C_4 perfluoroalkyl, arenesulfonyl, lower alkoxycarbonyl, or benzyloxycarbonyl, and,
wherein n = zero or one and p= zero or one with the proviso that n and p cannot both be equal to zero at the same time; and a pharmaceutically acceptable salt thereof.

Claims 2 to 16 related to further features of the compound of claim 1. Claims 17 and 18 were directed to pharmaceutical compositions comprising the compound of claims 1 to 16.

II. The Examining Division based their decision on documents

(1): Maryanoff, B.E. et al., J. Med. Chem., Vol.30, pages 880 to 887, 1987, and

(2): Bundgaard, H. and Larsen, J., J. Med. Chem., Vol.31, pages 2066 to 2069, 1988.

Their reasoning went as follows:

Document (1) was the closest prior art as it disclosed that 2,3:4,5-bis-O-(1-methylethylidene)-β-D fructopyranose sulfamate ie. the molecule, some of the claimed compounds were derived from, had anticonvulsant activity.

Starting from this prior art, the problem to be solved was to provide pharmaceutically active (anticonvulsant) derivatives of the fructopyranose sulfamate. The solution proposed was to mask the sulfamate portion by an imidate group which could be removed in a physiological medium to provide the parent compound.

Document (2) disclosed that sulfonyl imidates would act as prodrugs for drugs with a sulfonamide group and that prodrugs had advantageous properties over drugs. It, thus, provided the incentive for making imidate derivatives such as claimed and test them for their anticonvulsant properties.

The combined teachings of documents (1) and (2) would lead the skilled person to expect that a prodrug could be prepared from the fructopyranose sulfamate of document (1) by masking the sulfamate portion by an imidate group and that this prodrug would have the anticonvulsant activity of the parent compound. They rendered obvious the subject-matter of claim 1.

III. The Appellant's submissions were essentially as follows:

Documents (1) and (2) were selected from a search made with hindsight knowledge of the invention. Their combination was the result of an ex post facto analysis and did not indicate a genuine lack of inventive step.

The solution to the problem of providing further potentially improved anticonvulsant compounds by the provision of a **prodrug form** of the compound of document (1) was not obvious.

There were many possible modifications of the compound of document (1) which would have occurred to the skilled reader and, indeed, document (1) described a number of derivatives of said compound, but not a prodrug. Table 1 showed that the activity of the 2,3:4,5-bis-O-(1-methylethylidene)-β-D fructopyranose sulfamate was decreased by substitution at the sulphonamide N. This taught away from the invention.

None of the sulphonamide compounds disclosed in document (2) had any similarity to the fructopyranose imidate derivatives of the application in suit. Without experiment, it could not have been predicted that in vivo these derivatives would not be toxic, nor that they would undergo satisfactory hydrolysis to active sulphonamide.

For these reasons, the conclusion by the Examining Division of lack of inventive step of claim 1 in the light of the combined disclosure of documents (1) and (2) was unfounded.

IV. A communication according to Article 11(2) EPC of the rules of procedure of the Boards of Appeal was sent by the Board together with the summons to oral proceedings, setting out the Board's provisional, non-binding opinion.

V. The request for oral proceedings was withdrawn.

VI. The request in writing by the Appellant was that the decision under appeal be set aside and that a patent be granted on the basis of the claims as originally filed.

Reasons for the Decision

1. The appeal is admissible.

2. The closest prior art to the subject-matter of claim 1 is document (1). It discloses that 2,3:4,5-bis-O-(1-methylethylidene)-β-D fructopyranose sulfamate (ie. the molecule, from which some of the compounds of claim 1 are derived) has potent anticonvulsant activity. A study of some analogs thereof is carried out to ascertain those features associated with biological activity. It is found that derivatives carrying methyl or phenyl substitutions on the sulfamate group (Chart I, compounds 1 to 3) have an anticonvulsant activity lower than the fructopyranose sulfamate itself, or no anticonvulsant activity at all, as measured **in vivo** by the standard MES test carried out on mice.

3. Starting from document (1), the technical problem to be solved can be defined as providing derivatives of the 2,3:4,5-bis-O-(1-methyl ethylidene)-β-D fructopyranose sulfamate which afford at least as good an anticonvulsant activity as the parental fructopyranose sulfamate upon administration to a mammal.

4. The solution provided in claim 1 comprises derivatives in which the sulfamate portion of the 2,3:4,5-bis-O-(1-methylethylidene)-β-D fructopyranose sulfamate is masked by an imidate group.

5. The difference between the derivatives described in document (1) and the claimed compounds resides in the nature of the substitution on the nitrogen of the fructopyranose sulfamate, as the earlier derivatives are methyl or phenyl derivatives (see point 1, above) whereas the latter carry an imidate group.

6. Document (2) describes the advantages associated with chemically transforming drug substances into per se inactive derivatives (prodrugs), in particular, that the prodrug reconverts to the drug in vivo, so that the prodrug possesses, albeit indirectly, the same pharmaceutical properties as the drug, and, also, that the prodrug may be the solution to delivery problems due to e.g. unfavourable solubility and lipophilicity. In addition, document (2) discloses that **imidate derivatives** of sulfonamide drugs are prodrug forms of these drugs: on page 2067, it is found that imidate esters of p-toluenesulfonamide are hydrolysed in freshly prepared human plasma solutions; on page 2068, sulfonylimidate esters of phenols or of ethoxzolanide (used in the topical treatment of glaucoma) are cited as prodrugs.

7. Thus, at the priority date, the skilled person was aware from document (1) of the anticonvulsant activity of the fructopyranose sulfamate, and from document (2), that imidate derivatives of sulfonamide drugs would behave as prodrugs. In the Board's judgment, it was obvious when wanting to obtain derivatives of the fructopyranose sulfamate, while keeping the anticonvulsant activity, to combine the teachings of both these documents ie. to make N-sulfonyl imidate derivatives of said fructopyranose sulfamate.

8. The Appellant argued that such a combination could only be done with hindsight knowledge of the content of the application as filed. However, as the usefulness of transforming drugs into prodrugs in order to solve the type of problems solved in the instant application was already known as early as 1975 (references 1 to 3, page 2071 of document (2)), this argument cannot be accepted.

9. The fact that specific derivatives of fructopyranose sulfamate were found in document (1) to have low or no anticonvulsant activity was argued to teach away from the present invention. However, the skilled person aware of these results would, on the contrary, seek to make a different kind of chemical derivatives and in the light of document (2), would turn to isolating prodrugs as these would be expected to convert to the active parent drug in the body system.

10. The Board accepts that it could not be predicted with certainty whether, in vivo, imidate derivatives of fructopyranose sulfamate would be toxic or not, nor whether they would undergo satisfactory hydrolysis. Yet, the combined teachings of documents (1) and (2) would lead the skilled person in an obvious manner to make imidate derivatives and testing them would be a matter of routine as shown in document (1) which

discloses that the anticonvulsant activity test is a standard test dating from 1952 (page 881, right hand column, "Anticonvulsant testing"). There is, thus, no inventive activity linked to preparing or testing these compounds.

11. In view of the findings in points 7 to 10 above, the conclusion is reached that the subject-matter of claim 1 lacks inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

U. Bultmann U. Kinkeldey