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D E C I S I O N
of 25 March 2004

Case Number: T 1064/01 - 3.3.1

Application Number: 98114523.8

Publication Number: 0885880

IPC: C07C 317/44

Language of the proceedings: EN

Title of invention:
Sulfonylalkanoylamino hydroxyethylamino sulfamic acids useful as retroviral protease inhibitors

Applicant:
G.D. SEARLE & CO. and Monsanto Company

Opponent:
-

Headword:
Sulfamic acids/SEARLE, MONSANTO

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - alternative - effect not credible for all claimed compounds"

Decisions cited:
T 0939/92

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1064/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 25 March 2004

Appellant: G.D. SEARLE & CO.
P.O. Box 5110
Chicago, IL 60680-5110 (US)

Representative: Strych, Werner Dr.
Hansmann & Vogeser
Patent- und Rechtsanwälte
Postfach 70 08 60
D-81308 München (DE)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 29 May 2001 refusing European application No. 98114523.8 pursuant to Article 97(1) EPC.**

Composition of the Board:

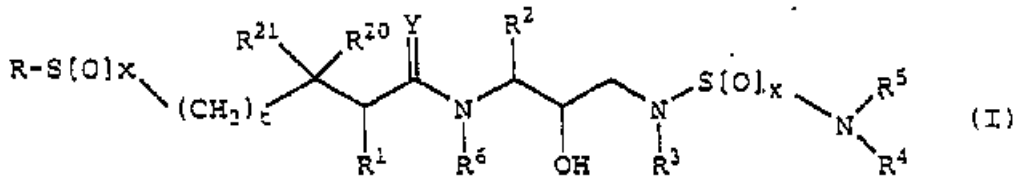
Chairman: A. J. Nuss
Members: R. Freimuth
J. H. Van Moer

Summary of Facts and Submissions

I. The appeal lodged on 3 July 2001 lies from the decision of the Examining Division posted on 29 May 2001 refusing European patent application No. 98 114 523.8 (European publication No. 885 880).

II. The decision under appeal was based on a main request comprising claims 1 to 13 as filed and on an auxiliary request comprising claims 1 to 7 as filed. Independent original claim 1 according to the then pending main and auxiliary request read as follows:

"1. A compound represented by the formula



(I)

or a pharmaceutically acceptable salt or ester thereof wherein:

R represents alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, alkoxyalkyl, aryl, aralkoxyalkyl, heteroaryl, aralkyl, heteroalkyl, heteroaralkyl, aminocarbonylalkyl, aminoalkyl, aminoalkylcarbonylalkyl, alkylcarbonylalkyl, aryloxyalkylcarbonyl, and aralkoxycarbonylalkyl radicals, aminoalkyl, and mono- and disubstituted aminoalkyl, mono- and disubstituted aminocarbonylalkyl and mono- and disubstituted aminoalkanoylalkyl radicals wherein the substituents are selected from alkyl, aryl aralkyl, cycloalkyl,

cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyalkyl radicals, or wherein said aminoalkyl, aminocarbonylalkyl and aminoalkanoylalkyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R^1, R^{20} and R^{21} independently represent hydrogen, $-CH_2SO_2NH_2$, $-CH_2CO_2CH_3$, $-CO_2CH_3$, $-CONH_2$, $-CH_2C(O)NHCH_3$, $-C(CH_3)_2(SH)$, $-C(CH_3)_2(SCH_3)$, $-C(CH_3)_2(S[O]CH_3)$, $-C(CH_3)_2(S[O]_2CH_3)$, alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, $-NO_2$, -CN, $-CF_3$, $-OR^9$ and $-SR^9$, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, aryloxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl,

heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3 or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical;

R^6 represents hydrogen and alkyl radicals;
each x independently represents 1 or 2;
t represents either 0, 1 or 2; and
Y represents O, S and NR^{15} wherein R^{15} represents hydrogen and radicals as defined for R^3."

III. The Examining Division found that the present application lacked inventive step pursuant to Article 56 EPC in view of document

(1) WO-A-92/08701.

The Examining Division held in particular that the compounds according to claim 1 differed from those described in claim 1, alternative (A1) and in claim 78 of the closest prior document (1) in substituting the sulfamoyl group for the carbamoyl group at the right-hand side of the core structure of the compounds. As the known compounds were retroviral protease inhibitors, the problem underlying the application was seen in providing alternative compounds having that particular

activity. Activity data were only given for one compound according to claim 1 in the application as filed, namely on Table 9, and for one other compound in the parent application. However, there was no evidence on file that all the hugely disparate groups listed for all the variables in present claim 1 also gave rise to compounds having retroviral protease inhibitory activity since small variations in the chemical structure could lead to a loss of activity. Compounds for which it was not credible that they had the activity ascribed to them were not inventive (see T 939/92, OJ EPO 1996, 309).

IV. At the oral proceedings before the Board held on 25 March 2004, the Appellant (Applicant) submitted a sole request consisting of 35 claims. Independent claim 1 thereof is identical to original claim 1 and, thus, to that in the decision under appeal.

The Appellant argued that the closest prior document (1) did not suggest varying the right-hand side of the core structure of the compounds described therein while maintaining the retroviral inhibitory activity. In particular, that document did not hint to substitute the sulfamoyl group present in the claimed compounds for the carbamoyl group present in the known compounds without loss of that activity. Small structural modifications in the compounds could entail sharp changes in their biological activity. Moreover, the carbonyl group and the sulfonyl group were chemically and structurally different, including molecular volume, spatial orientation, capacity for hydrogen bonding and electro negativity, such that the skilled person would not have expected this structural variation to leave

the biological activity unaffected. In support thereof, the Appellant provided an activity test report of two compounds differing from each other exclusively in their carbonyl and sulfonyl group, respectively. He indicated that both compounds did not fall within the scope of claim 1. The structural change made to the known compounds was not obvious and consequently the activity shown by the claimed compounds was not to be expected.

The Appellant argued furthermore that the retroviral inhibitory activity of compounds having the claimed structure was proven. The compounds claimed were of a new structural type, namely comprising a sulfonyl group at the right-hand side thereof; therefore the activity shown for some claimed compounds could be generalised to any compound claimed having that particular structure. Thus, the Appellant had the right to claim a large protection of his invention for preventing competitors interfering therewith. That right resulted necessarily in a broad scope of the claims.

V. The Appellant requested that the decision under appeal be set aside and that the application be granted on the basis of the request consisting of claims 1 to 35 submitted at the oral proceedings.

VI. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Inventive step*

The sole issue arising from this appeal consists in deciding whether or not the subject-matter of claim 1 according to the main request or according to the auxiliary requests 1 to 4 involves an inventive step.

2.1 Claim 1 is directed to sulfonylalkanoylamino hydroxyethylamino sulfamic acids showing retroviral protease inhibitor activity. Similar compounds having the identical activity already belong to the state of the art. Document (1), in particular claim 1, alternative (A1) and claim 78, relates to sulfonylalkanoylamino hydroxyethylamino carbamic acids which are specified to inhibit retroviral protease (page 1, lines 7 and 8, claims 68 and 118).

For these reasons, the Board considers, in agreement with the Appellant and the Examining Division, that the disclosure of document (1) specified above represents the closest state of the art, and, hence, the starting point in the assessment of inventive step.

2.2 In view of this state of the art the problem underlying the present application as submitted by the Appellant in examination and appeal proceedings, and as indicated in the application as filed on page 3, paragraph 2 consists in providing further compounds having retroviral protease inhibitory activity.

2.3 The application in suit proposes as the solution to this problem the compounds according to claim 1 having the general formula (I) (see point II above) which are

characterized by the presence of a sulfonyl group at the right-hand side of the molecule.

2.4 To support his submission that the claimed compounds show in fact the alleged retroviral protease inhibitory activity and, thus, successfully solve the problem as defined in point 2.2 above (see decision T 939/92, *loc. cit.*, point 2.6), the Appellant referred to the activity tests of two individual compounds covered by claim 1, the one comprised in the application as filed on Table 9 and the other addressed on page 3 of the Appellant's letter dated 25 February 2004.

2.4.1 The activity reports tested two individual compounds having a chemical structure according to general formula (I) of present claim 1. In both compounds the substituent R is the CH_3-group, R^1 the CH_3-group, R^2 the benzyl group, R^3 the 2-methylpropyl group, R^6 hydrogen, R^{20} hydrogen, R^{21} hydrogen and Y oxygen, the index x is 2 and T is 0 and the stereochemical configuration of the CH_3-group for the substituent R^1 is S, of the benzyl group for R^6 is S and of the OH-substituent is R. Both individual compounds differ from each other exclusively in their substituents R^4/R^5 which are either hydrogen and a tert. butyl group or both a methyl group.

Thus, the Appellant has provided evidence in support of the purported inhibitory activity, i.e. test reports, exclusively for a very narrow sector of the claimed invention: both compounds tested have the identical chemical structure apart from a minor variation of the substituents R^4/R^5 thereby covering merely a very particular substitution pattern within formula (I) of claim 1. The substitution pattern common to both

compounds fits in general formula (I) only the generic group alkyl for the substituents R, R^1 and R^3, aralkyl for the substituent R^2, hydrogen for the substituents R^6, R^{20} and R^{21} and oxygen for the substituent Y, the numbers 2 and 0 for the indices x and t, respectively, and the specific stereochemical configuration [SSR].

2.4.2 However, the purported technical effect, in the present case the particular inhibitory activity, can only justify the inventive ingenuity of the claimed compounds if it would be credible that substantially **all** claimed compounds possessed this activity (see decision T 939/92, *loc. cit.*, point 2.5.4). Therefore, it must be examined whether or not the Appellant's extrapolation of the presence of a retroviral protease inhibitory activity from the two tested compounds to any untested compound **within the whole area claimed**, in the Board's judgement, is credible.

2.4.3 The Appellant submitted in the context of inventive step that the inhibitory activity of the claimed compounds was not predictable starting from those of the closest prior document (1) since small structural modifications thereof may entail strong effects on the presence or absence of an inhibitory activity (see also decision under appeal, point 4 of the reasons). However, that argument cannot be valid only for the structural modification of the claimed compounds vis-à-vis the compounds known from the state of the art, but for reasons of consistency it must also be valid within the whole area claimed. Thus, small structural modifications applied to the tested compounds render no longer predictable the activity of such modified compounds, however, still covered by claim 1. Therefore,

there is no support for the Appellant's projection of the retroviral protease inhibitory activity from the two tested compounds according to claim 1, wherein the substituents R and R^3 each mean an alkyl group (see point 2.4.1 above), to claimed compounds wherein these substituents mean any other group of the lists of 24 and 17 alternative generic groups given in claim 1, respectively. These alternative generic groups listed in claim 1 comprise *inter alia* heteroaryl groups which are structurally completely different to the alkyl group comprised in the tested compounds. Relying on the Appellant's submission that the influence of structural modifications on the desired inhibitory activity is unpredictable, it does not appear credible, in the Board's judgement, that the retroviral inhibitory activity of claimed compounds having two alkyl substituents could be extrapolated to those compounds within claim 1 having for example two - structurally different - heteroaryl groups.

For that reason, the Appellant cannot successfully rely on the activity tests presented as evidence for the alleged presence of a retroviral protease inhibitory activity of **all** the claimed compounds.

2.4.4 The Appellant argued that the compounds claimed were of a new structural type, namely comprising a sulfonyl group on their right-hand side. This fact is correct and may support the unity of this invention but has nothing to do with the issue addressed in points 2.4.1 to 2.4.3 above, namely whether or not the alleged inhibitory activity is credibly present within the whole area claimed.

When questioned by the Board on that point at the oral proceedings, the Appellant pointed neither to any further reason nor to corroborating evidence for his view that the activity shown for some claimed compounds could be generalised to any compound claimed. Therefore, the Appellant's view is based on mere speculation which the Board cannot sanction.

2.5 For these reasons and on the basis of the evidence on file, the Board is **not** satisfied that substantially **all** claimed compounds show a retroviral protease inhibitory activity. However, a reformulation of the problem of providing further compounds having retroviral protease inhibitory activity (cf. point 2.2 above)is not possible as the Appellant neither submitted that there existed any less ambitious problem, nor is the Board able to identify such less ambitious problem for itself. Since only those of the claimed compounds could possibly involve an inventive step which could be accepted as solutions of the technical problem underlying the invention of providing further compounds having retroviral protease inhibitory activity (see decision T 939/92, *loc. cit.*, point 2.7 of the reasons), the subject-matter of claim 1 extends to compounds which are not inventive in the sense of Article 56 EPC.

3. As a result, the Appellant's request is not allowable.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. Nuss