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**Datasheet for the decision
of 6 December 2006**

Case Number: T 0358/04 - 3.3.01

Application Number: 96940302.1

Publication Number: 0861249

IPC: C07D 405/12

Language of the proceedings: EN

Title of invention:

Substituted Sulfonylalkanoylamino Hydroxyethylamino
Sulfonamide Retroviral Protease Inhibitors

Applicant:

G.D. Searle LLC.

Opponent:

-

Headword:

Retroviral protease inhibitors/G.D. SEARLE

Relevant legal provisions:

EPC Art. 54, 56, 111(1), 123(2)

Keyword:

"Amendments allowable (yes)"

"Novelty (yes)"

"Inventive step (yes) - non obvious further compounds as
retroviral protease inhibitors"

Decisions cited:

G 0005/83, T 0852/91

Catchword:

-



Case Number: T 0358/04 - 3.3.01

DECISION
of the Technical Board of Appeal 3.3.01
of 6 December 2006

Appellant: G.D. Searle LLC.
P.O. Box 5110
Chicago
Illinois 60680-5110 (US)

Representative: Strych, Werner Maximilian Josef
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 19. August 2003
refusing European application No. 96940302.1
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. Nuss
Members: P. Ranguis
J. Van Moer

Summary of Facts and Submissions

I. An appeal was lodged by the Applicant against the decision of the Examining Division posted on 19 August 2003 to refuse under Article 97(1) EPC the European patent application No. 96 940 302.1 (European publication No. 0 861 249) stemming from the International patent application No. PCT/US96/17771.

II. The decision under appeal was based on two sets of claims, respectively main request and first auxiliary request. The Examining Division held that the subject-matter of Claim 1 of the main request and first auxiliary request extended beyond the content of the application as originally filed. Furthermore, the subject-matter of Claim 9 of both the main request and the first auxiliary request did not involve an inventive step in view of the teaching of documents

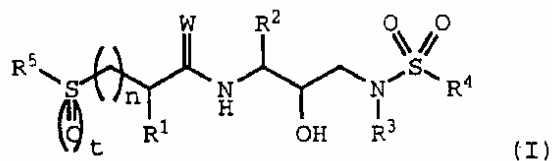
(1) WO-A-94 04493

(2) WO-A-94 10136

III. With the statement of grounds of appeal, the Appellant submitted as sole request a fresh set of twenty two claims.

At the oral proceedings before the Board which took place on 6 December 2006, the Appellant abandoned its previous request and submitted as main request a set of nineteen claims. Independent Claims 1, 10, 11, 13, 15, 17 and 19 read as follows:

"1. Compound represented by the formula:



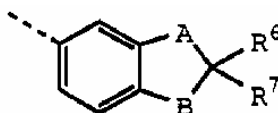
of a pharmaceutically acceptable salt, prodrug or ester thereof, wherein n and t each independently represent 0, 1 or 2; W represents O or S;

R¹ represents hydrogen, alkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cyanoalkyl, -CH₂CONH₂, -CH₂CH₂CONH₂, -CH₂S(O)₂NH₂, -CH₂SCH₃, -CH₂S(O)CH₃ or -CH₂S(O)₂CH₃ radicals;

R² represents alkyl, aralkyl, alkylthioalkyl, arylthioalkyl or cycloalkylalkyl radicals;

R³ represents alkyl, cycloalkyl or cycloalkylalkyl radicals;

R⁴ represents a radical of the formula

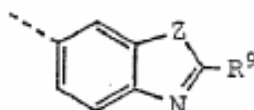


wherein A and B each independently represent O, S, SO or SO₂;

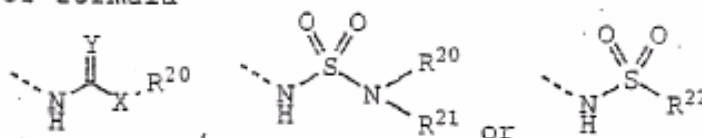
R⁶ represents deuterium, alkyl or halogen radicals; and

R⁷ represents hydrogen, deuterium, alkyl or halogen radicals; or

R⁴ represents a radical of the formula



wherein Z represents O, S or NH; and R⁹ represents a radical of formula



wherein Y represents O, S or NH; X represents a bond, O or NR²¹;

R²⁰ represents hydrogen, alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, heterocycloalkyl, aminoalkyl, N-mono-substituted or N,N-disubstituted aminoalkyl wherein said substituents are alkyl, aralkyl, carboxyalkyl, alkoxyalkyl, cyanoalkyl or hydroxyalkyl radicals; or XR²⁰ represents radicals of hydroxymethyl, aminomethyl, N-mono-substituted or N,N-disubstituted aminomethyl wherein said substituents are alkyl, aralkyl, carboxyalkyl, alkoxyalkyl, cyanoalkyl or hydroxyalkyl radicals;

R²¹ represents hydrogen or alkyl radicals; or the radical of formula -NR²⁰R²¹ represents a heterocyclo radical; and

R²² represents alkyl or R²⁰R²¹N-alkyl radicals; and

R⁵ represents heteroaryl or heterocyclo radicals each of which is coupled via a ring carbon atom, or alkyl radical substituted with R¹⁰, cycloalkylamino, aralkylamino, aminoalkoxycarbonyl, (alkylamino)alkoxycarbonyl, (dialkylamino)alkoxycarbonyl, (aminocarbonyl)(alkoxycarbonyl)methyl or bis(aminocarbonyl)methyl radicals or 1 or more radicals of amino, alkylamino or dialkylamino or 2 or more radicals of hydroxy or alkoxy; and

R¹⁰ represents heteroaryl, heterocyclo, alkoxy carbonyl, aryl carbonyl, cycloalkyl carbonyl, heteroaryl carbonyl or heterocyclo carbonyl radicals; or R¹⁰ represents R¹¹R¹²N-C(O)- radical, wherein

R¹¹ represents heteroaryl, heterocyclo, heteroaralkyl, heterocycloalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, cycloalkylaminoalkyl, aralkylaminoalkyl or diaminoalkyl radicals; and

R¹² represents hydrogen or alkyl radicals."

"10. Composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier."

"11. Use of a compound of Claim 1 for preparing a medicament for inhibiting a retroviral protease."

"13. Use of a composition of Claim 10 for preparing a medicament for treating a retroviral infection."

"15. Use of a compound of Claim 1 for preparing a medicament for preventing replication of a retrovirus."

"17. Use of a compound of Claim 1 for preparing a medicament for preventing replication of a retrovirus *in vitro*."

"19. Use of a composition of claim 10 for preparing a medicament for treating AIDS."

The Appellant also filed an auxiliary request.

IV. The Appellant submitted at the oral proceedings the following arguments.

The compounds of the claimed subject-matter were novel as they differed from those disclosed in document (1) in that the substituent R⁴ of this document was not a phenyl group fused with a heterocycle as set out in Claim 1.

Regarding inventive step, document (1) taught that a compound wherein R⁴ was a p-methoxy phenyl radical (see example 2) showed an inhibition of the HIV protease higher than the compound wherein R⁴ was a 3,4-dimethoxy phenyl (see example 12), i.e. IC₅₀ (nanomolar) of 3.2 and 38 respectively (see Table 9). The person skilled in the art would have, therefore, been deterred to design other compounds having two adjacent alkoxy substituents such as a benzodioxol-5-yl for their activities as retroviral protease inhibitors.

- V. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the main request submitted at the oral proceedings or, in the alternative, on the basis of the auxiliary request also submitted at the oral proceedings.
- VI. At the end of the oral proceedings the decision of the Board was announced.

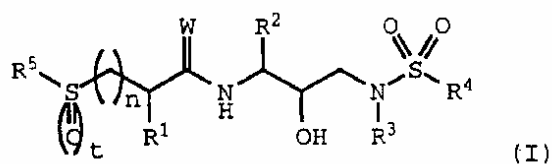
Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Amendments*

2.1 Compared to Claim 1 as originally filed the subject-matter of present Claim 1 was restricted to a compound of the formula



(see point III above)

wherein some of the meanings of R⁴, i.e. aryl, heteroaryl or heterocyclo were deleted. This amendment represents a simple limitation of the subject-matter originally claimed which does not generate novel subject-matter and is, therefore, admissible.

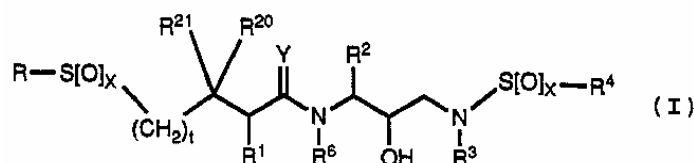
2.2 Compared to Claim 2 as originally filed the subject-matter of present Claim 2 was restricted to a compound of Claim 1, wherein some of the meanings of R⁴, i.e. aryl, benzofused 5 to 6 member heteroaryl or benzo fused 5 to 6 ring member heterocyclo were deleted. Compared to Claim 3 as originally filed the subject-matter of present Claim 3 was restricted to a compound of Claim 2, wherein some of the meanings of R⁴, i.e. aryl, benzofused 5 to 6 member heteroaryl or benzo fused 5 to 6 ring member heterocyclo were deleted. Those amendments also represent an admissible limitation of the subject-matter originally claimed. The subject-matter of the present Claim 4 corresponds to the subject-matter of Claim 4 as originally filed.

- 2.3 Compared to Claim 5 as originally filed the subject-matter of present Claim 5 was restricted to a compound of Claim 4 wherein the meanings of R⁴, i.e. phenyl, 2-naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, 3,4-dimethoxyphenyl, 3-aminophenyl, 4-aminophenyl, benzothiazol-5-yl, benzothiazol-6-yl, 2-amino-benzothiazol-5-yl, 2-(methoxycarbonylamino) benzothiazol-5-yl, 2-amino-benzothiazol-6-yl, 2-(methoxycarbonylamino) benzothiazol-6-yl, 5-benzoxazolyl, 6-benzoxazolyl, 6-benzopyranyl, 3,4-dihydrobenzopyran-6-yl, 7-benzopyranyl, 3,4 dihydrobenzopyran-7-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,4-benzodioxan-6-yl, 5-benzimidazolyl, 2-(methoxycarbonylamino) benzimidazol-5-yl, 6-quinolinyl, 7-quinolinyl, 6-isoquinolinyl or 7-isoquinolinyl were deleted. This amendment represents an admissible limitation of the subject-matter originally claimed.
- 2.4 Compared to Claim 6 as originally filed the subject-matter of present Claim 6 was restricted to a compound of Claim 5 wherein the meanings of R⁴, i.e. phenyl, 2-naphthyl, 4-methoxyphenyl, 4-hydroxyphenyl, benzothiazol-5-yl, benzothiazol-6-yl, benzoxazol-5-yl, 2,3-dihydrobenzofuran-5-yl, benzofuran-5-yl, 1,4-benzodioxan-6-yl, 2-(methoxycarbonylamino) benzothiazol-5-yl, 2-(methoxycarbonylamino) benzothiazol-6-yl, 2-(methoxycarbonylamino) benzimidazol-5-yl were deleted. This amendment represents an admissible limitation of the subject-matter originally claimed.

- 2.5 The subject-matter of the present Claims 7, 8 and 10 corresponds to the subject-matter of Claims 7, 8 and 10 as originally filed respectively.
- 2.6 Present Claim 9 is a list of individual compounds disclosed in Claim 9 as originally filed.
- 2.7 The subject-matter of Claims 11 to 19 relates to the use of a compound or composition for preparing a medicament worded in the non-objectionable form (see G 5/83 OJ EPO 1985, 64, Order 2.). This subject-matter indeed finds support in Claims 11 to 19 as originally filed respectively which related to therapeutic methods claims (see G 5/83 op.cit, Order 1.).
- 2.8 The amendments, therefore, do not raise any objection under Article 123(2) EPC.

3. *Novelty*

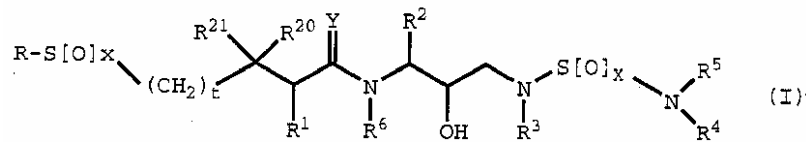
- 3.1 Document (1) discloses sulfonylalkanoylamino hydroxyethylamino sulfonamides useful as retroviral protease inhibitors of formula



wherein R^4 can *inter alia* represent an aryl radical. The term "aryl" means a phenyl or naphthyl radical optionally substituted by one or more alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl (see page 5, lines 2 and 11 and page 8, lines 8 to 11) and x may be 2 (see page 4, line 12).

The claimed subject-matter distinguishes from the subject-matter of that document in that R⁴ is a phenyl **fused with a 5 ring member heterocyclo radical** of formula set out in Claim 1 (see point III above) and not a phenyl substituted by **univalent radicals**. Claim 1 is, therefore, novel in view thereof. This conclusion also applies to Claims 2 to 19.

3.2 Document (2) discloses sulfonylalkanoylamino hydroxyethylamino sulfamic acids useful as retroviral protease inhibitors of formula



wherein R⁴ and R⁵ may together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical (see page 5, lines 14 to 17) and x may be 2 (see page 5, line 21).

The claimed subject-matter distinguishes from that document in that R⁴ is a **phenyl fused with a 5 ring member heterocyclo radical** of formula set out in Claim 1 (see point III above) and not an **heteroaryl** radical. Claim 1 is, therefore, novel in view thereof. This conclusion also applies to Claims 2 to 19.

3.3 There is, therefore, no objection of lack of novelty in the sense of Article 54 EPC.

4. *Inventive step*

4.1 The present claimed subject-matter relates to sulfonylalkanoylamino hydroxyethylamino sulfonamides

useful as medicaments for inhibiting retroviral proteases (see page 1, lines 6 to 10).

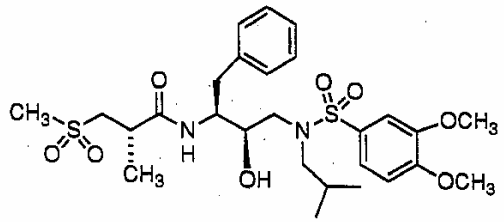
- 4.2 In agreement with the Examining Division and the Appellant, the Board considers that whereas both documents (1) and (2) aim at the same objective (see points 3.1 and 3.2 above), document (1) is the closest state of the art for defining the technical problem to be solved given that the compounds disclosed therein comprise an **aryl** sulfonamide radical, i.e. $-S[O]_x-R^4$ when x is 2 (see point 3.1 above).
- 4.3 The technical problem in view thereof may be viewed in the provision of further compounds inhibiting retroviral proteases.
- 4.4 In view of the description, in particular, the biological tests (see pages 234 to 243), the Board has no reason to doubt that the technical problem is solved within the whole area, namely that the claimed compounds are effective retroviral inhibitors.
- 4.5 It remains to be decided whether or not the claimed solution is obvious in view of the prior art cited.
- 4.5.1 Starting from document (1), the question arises, in particular, whether the person skilled in the art would have been directed to expect that the sulfonylalkanoylamino hydroxyethylamino sulfonamides of formula (I) wherein R^4 is modified as now defined in Claim 1 would have solved the technical problem defined above.

4.5.2 First, in the Board's judgment, in view of the general teaching of document (1) that R^4 may be phenyl substituted by one or more alkoxy radicals (see point 3.1 above), the person skilled in the art could have expected that a compound wherein R^4 is a m-, p-dialkoxyphenyl group would have shown an activity as retroviral protease inhibitors.

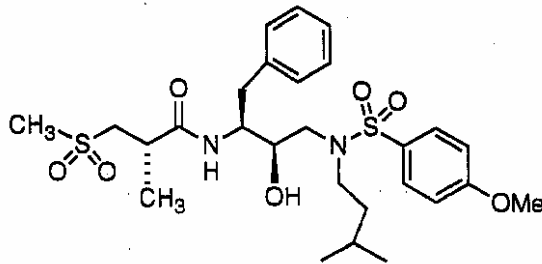
4.5.3 However, to deny inventive step for novel chemical compounds because of their "structural similarity" to known chemical compounds would be justified, if the skilled person knew, be it from common general knowledge, or from some specific disclosure, that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on those properties which are important for solving the technical problem underlying the invention (see T 852/91 of 6 June 1994, point 8.2). In the present case, there is no hint in document (1) to replace a m, p-dialkoxy phenyl radical by a benzodioxolyl radical to solve the above defined technical problem.

Document (2) cannot rebut that finding since it discloses compounds wherein the group attached to the sulphonamide moiety is heterocycloalkyl or a heteroaryl radical (see point 3.2 above). Such a document gives also no hint in the direction of the present claimed subject-matter to solve the above defined technical problem.

4.5.4 Furthermore, as pointed out by the Appellant (see point IV above), the person skilled in the art would have noted that the compound of example 12 of formula



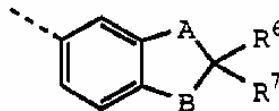
wherein R⁴ is a m-,p-dimethoxyphenyl group, was more than ten times less active in inhibiting the HIV protease than the compound of example 2 of formula



wherein R⁴ is a p-methoxyphenyl group (see pages 77-78, example 16, Table 9).

In view of the above, the person skilled in the art would certainly not have been induced to pursue in that non-promising direction and the Board does not see any reason for the skilled person to try compounds wherein the two alkoxy groups in the meta and para position are attached together to form a divalent radical.

4.5.5 It derives therefrom that in view of the teaching of documents (1) and (2), the person skilled in the art would not have been induced to design in an obvious manner compounds of formula (I) as claimed wherein R⁴ corresponds to a group of formula



wherein A and B represent O as defined in Claim 1 (see point III above). The other meanings of R⁴ defined in the claimed subject-matter are still more remote from

the disclosure of document (1) and the person skilled in the art would have had still less reason to design them to solve the above technical problem.

4.6 In view of the above, Claim 1 involves an inventive step over the prior art cited. The same applies to dependent Claims 2 to 9 which represent particular embodiments of the subject-matter of Claim 1. Claim 10 relating to a composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier is based on the same inventive concept and derives its patentability on the same basis as does Claim 1. Claims 11 to 19 relating to the use of the claimed compounds for preparing medicament having a specific activity are based on the same inventive concept and derive their patentability on the same basis as does Claim 1.

4.7 In conclusion the main request before the Board complies with the requirements of Article 56 EPC.

Auxiliary request

5. The main request being allowable for the reasons set out above, there is no need for the Board to decide on this request.

6. Article 111(1) EPC - Remittal to the first instance

Although the Board has come to the conclusion that the main request was to be allowed, it was noted that the description had still to be brought into conformity with the claims of the present request. Therefore, 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 exercises its discretion under Article 111(1) EPC to remit the case to the first instance in order for the description to be adapted to the allowable claimed subject-matter according to the main request submitted before the Board at the 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 first instance with the order to grant a patent on the basis of
 - Claims 1 to 19 filed during the oral proceedings, and a description yet to be adapted.

The Registrar

The Chairman

N. Maslin

A. Nuss