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D E C I S I O N
of 21 September 2004

Case Number: T 0318/02 - 3.3.1

Application Number: 96901556.9

Publication Number: 0765307

IPC: C07C 317/18

Language of the proceedings: EN

Title of invention:
N alpha-2-(4-nitrophenylsulfonyl)ethoxycarbonyl-amino acids

Patentee:
Hyundai Pharm. Ind. Co., Ltd.

Opponent:
Avecia Limited

Headword:
Protected amino acids/HYUNDAI PHARM

Relevant legal provisions:
EPC Art. 56

Keyword:
"Main and first to third auxiliary request: inventive step (no) obvious to try with a reasonable expectation of success"

Decisions cited:
T 0595/90, T 0288/98

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0318/02 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 21 September 2004

Appellant: (Opponent)	Avecia Limited P.O. Box 42 Hexagon House Blackley Manchester M9 8ZS (GB)
Representative:	Revell, Christopher Avecia Limited Intellectual Property Group P.O. Box 42 Hexagon House Blackley Manchester M9 8ZS (GB)
Respondent: (Proprietor of the patent)	Hyundai Pharm. Ind. Co., Ltd. 1110-2, Hwagok-dong, Gangseu-gu Seoul 157-019 (KR)
Representative:	Turi, Michael, Dipl.-Phys. Samson & Partner Widenmayerstrasse 5 D-80538 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 15 January 2004 concerning maintenance of European patent No. 0765307 in amended form.**

Composition of the Board:

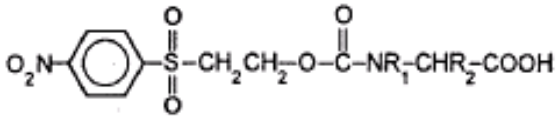
Chairman: R. Freimuth
Members: P. F. Ranguis
R. T. Menapace

Summary of Facts and Submissions

I. The Appellant (Opponent) lodged an appeal against the interlocutory decision of the Opposition Division to maintain the European patent No. 765 307 (European application No. 96 901 556.9) in the form as amended pursuant to Article 102(3) EPC.

II. The patent in suit in the form as amended comprised eight claims. Claim 1 had the same wording as Claim 1 as granted and read as follows:

"1. N^{α}-2-(4-nitrophenylsulfonyl)ethoxycarbonyl-amino acids having the general formula:



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wherein, R_1 represents hydrogen atom, and R_2 represents isopropyl, 2-methylpropyl, 2-methylthioethyl, benzyl, carboxamido-methyl, 2-carboxamidoethyl, 4-tert-butoxybenzyl, indolyl-3-methyl, S-(triphenylmethyl)thiomethyl, 1-(triphenylmethyl)imidazolyl-4-methyl, 3-(N^{G}-mesitylenesulfonyl)guanidinopropyl, N-xanthylcarboxamidomethyl, 2-(N-xanthylcarboxamido)ethyl or S-(acetamidomethyl)thiomethyl; or R_1 and R_2 together represent propylene radical".

III. Notice of opposition had been filed by the Appellant, requesting revocation of the patent in its entirety on the ground of lack of novelty or inventive step in view of the cited prior art.

IV. The Opposition Division held that although the claimed N^{α}-Nsc protected amino acid derivatives might have been considered obvious in view of document

(1) Tetrahedron Letters, 35, No. 42, 7821-7824, (1994),

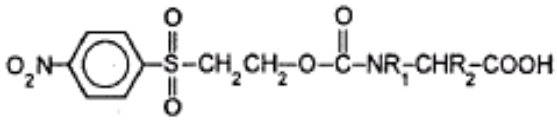
representing the closest state of the art, the production of the claimed compounds could not be achieved by the methods disclosed in document (1). The failure of the processes of document (1) suggested that the claimed compounds were not viable alternatives. Since the methods of preparation claimed in the then pending request were the first to achieve this result and did so in an inventive manner, the claimed compounds became non-obvious. The decision T 595/90 (OJ EPO 1994, 695) was cited in that respect.

V. In response to a communication of the Board, the Respondent (Proprietor of the patent) filed as first auxiliary request a fresh set of claims which comprised the same Claim 1 as in the set of claims maintained by the Opposition Division, namely Claim 1 as granted (cf. point II above).

VI. At the oral proceedings before the Board which took place on 21 September 2004, the Appellant filed as second and third auxiliary requests two fresh sets of Claims:

Claim 1 of the second auxiliary request read as follows:

"1. N^{α}-2-(4-nitrophenylsulfonyl)ethoxycarbonyl-amino acids having the general formula:



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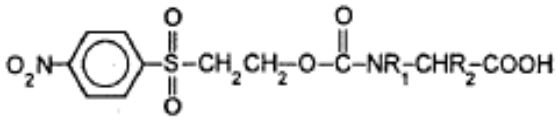
wherein, R_1 represents hydrogen atom, and R_2 represents carboxamido-methyl, 2-carboxamidoethyl, N-xanthylcarboxamidomethyl, or 2-(N-xanthylcarboxamido)ethyl".

Claim 1 of the third auxiliary request read as follows:

"1. N^{α}-2-(4-nitrophenylsulfonyl)ethoxycarbonyl-amino acids having the general formula:



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wherein, R_1 represents hydrogen atom, and R_2 represents S-(triphenylmethyl)thiomethyl, 1-(triphenylmethyl)imidazolyl-4-methyl or S-(acetamidomethyl)thiomethyl".

VII. In the written proceedings and at the oral proceedings, the Appellant submitted that the disclosure of document (1) was not limited to the specific N^{α}-Nsc-protected amino acids disclosed therein but taught more generally the valuable properties of the N^{α}-Nsc-protected amino acids in solid phase peptide synthesis (cf. page 7824, conclusion). The person skilled in the art would have been, therefore, directed in an obvious manner to apply the teaching of document (1) to design the Nsc-protected amino acids derivatives of Claim 1 for solid phase peptide synthesis.

Contrary to the Respondent's opinion, the disclosure of document (1) did not only teach methods which yielded the N^{α}-Nsc-protected amino acids but provided a broad range of purification methods applicable for purifying the prepared N^{α}-Nsc-protected amino acids.

At the oral proceedings before the Board, the Appellant withdrew his request for reimbursement of the appeal fee pursuant to Article 113(1) EPC.

VIII. In the written proceedings and at the oral proceedings, the Respondent submitted the following arguments:

The technical problem to be solved in view of document (1) was to provide further N^{α}-protected amino acids useful in solid phase peptide synthesis, stable in solid form and in form of solutes, in particular at elevated temperature (e.g. 40°C), avoiding or at least minimizing racemization in the peptide synthesis and useful for industrial purposes.

The experiments provided as document

(8) Comparison of stability for dissolved Nsc- and Fmoc-amino acids

showed that the N^{α}-Nsc-protected amino acids of Claim 1 taken as a whole revealed, on the one hand, a better stability in DMF or NMP than the different N^{α}-Nsc-protected amino acids disclosed in document (1). On the other hand, document (8) showed that the N^{α}-Nsc-protected amino acids of Claim 1 revealed a better stability than the corresponding N^{α}-Fmoc-protected amino acid derivatives in DMF or NMP, in particular at

elevated temperature (e.g. 40°C). This surprising stability opened the possibility of using those amino acids in automatic synthesizers or in a convergent peptide synthetic strategy or, more importantly, rendered feasible a solid phase peptide synthesis in an aprotic polar solvent at elevated temperature.

Document

(11) J. Peptide Res. **56**, 63-69 (2000)

showed that the N^{α}-Nsc-protected amino acids Cys and His suffered a smaller racemization than the corresponding N^{α}-Fmoc-protected amino acids in peptide synthesis.

In view of document

(2) Recl. Trav. Chim. Pays-Bas **107**, 621-626 (1988)

which reported that Nsc-D,L-Phe-OMe was unstable in neutral solvent, the person skilled in the art would have expected that at least some of the amino acid derivatives of Claim 1 would have been unstable and, therefore, the observed stability was unexpected.

The experiments submitted as document

(7) Declaration of Vladimir. V. Samukov, dated 10 December 2001

showed that the N^{α}-Nsc-protected amino acids defined in Claim 1 other than asparagine and glutamine derivatives, could be prepared by the Bolin method with poor to relatively good yields, depending on the amino acids

involved, but asparagine and glutamine derivatives could not be obtained at all. Furthermore, the yields of N^{α}-Nsc-asparagine and N^{α}-Nsc-glutamine derivatives were below 5%, with very poor purities, when these two protected amino acids were prepared exactly according to the Schotten-Baumann process as disclosed in document (1). Such a production was not of industrial usefulness as a starting material for peptide synthesis.

The processes defined in any of the present requests were the first to achieve the preparation of the N_{α}-Nsc-protected amino acids defined in Claim 1 of those requests and did so in an inventive manner, so that the subject-matter of Claim 1 of these requests was also inventive as held in the decision T 595/90 (loc.cit.).

IX. The Appellant requested that the decision under appeal be set aside and that the patent be revoked.

The Respondent requested that the appeal be dismissed or that the patent be maintained on the basis of either the first auxiliary request filed on 24 August 2004, or the second or third auxiliary request filed during oral proceedings.

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

Reasons for the Decision

1. The appeal is admissible.

Main and first auxiliary request

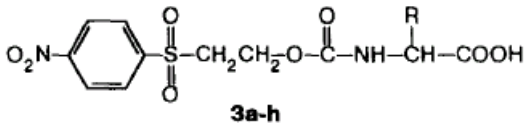
2. *Article 56 EPC - Inventive step*

2.1 Independent Claim 1 according to the main request and Claim 1 according to the first auxiliary request are identical; it is Claim 1 as granted (cf. points II and V above). Therefore the Board's considerations having regard to the inventive step of that claim as well as the conclusion drawn therefrom necessarily apply to either request and it is proper to consider both requests together.

2.2 Claim 1 relates to N^{α}-Nsc-protected amino acids useful for solid phase peptide synthesis (cf. patent in suit, page 2, lines 3 to 24). The abbreviation "Nsc" is used to designate the 2-(4-nitrophenylsulfonyl)ethoxycarbonyl group.

2.3 The Board concurs with both parties that document (1) is the closest state of the art to start from in the assessment of inventive step.

That document reports the synthesis of N^{α}-Nsc-protected L-amino acids **3a-h** and their usefulness in the solid phase synthesis of peptides:



3a-h

a: R = H
b: R = CH_3
c: R = $CH(CH_3)CH_2CH_3$
d: R = CH_2OBu^t
e: R = $CH(CH_3)OBu^t$
f: R = $(CH_2)_4NHCOOBu^t$
g: R = CH_2COOBu^t
h: R = $CH_2CH_2COOBu^t$

Two methods of preparation were disclosed. The acylation of amino acids with Nsc-Cl under usual Schotten-Baumann conditions gave the corresponding Nsc derivatives in low to moderate yields and the resulting N^{α}-Nsc amino acids **3** could be isolated in a pure form only by chromatography on a silica gel column. The acylation of trimethylsilyl derivatives of amino acids in non-aqueous solutions according to the method of Bolin et al led to markedly better results (cf. page 7821, third paragraph to page 7822). Prepared N^{α}-Nsc amino acids **3a-h** were used in the synthesis of the dodecapeptide Ala-Ser-Ser-Thr-Ile-Ile-Lys-Glu-Gly-Ile-Asp-Lys (cf. page 7823, second paragraph). It was found, in conclusion, that Nsc-amino acids appeared to be suitable intermediates for the solid phase peptide synthesis under conditions very similar to that used for 9-fluorenylmethoxycarbonyl (Fmoc) derivatives (cf. page 7824, second paragraph).

2.4 Starting from document (1) as the closest prior art, the technical results or effects successfully achieved by the claimed subject-matter vis-à-vis that prior art are to be determined for defining the technical problem to be solved by the invention. To this end, the Respondent referred to an alleged improvement in stability of the claimed compounds.

2.4.1 The experiments provided by the Respondent as document (8) compare the stability in DMF or in NMP, at 40°C after 8-10 days, on the one hand, of the claimed N^{α}-Nsc-protected amino acids vis-à-vis the N^{α}-Nsc-protected amino acids **3** disclosed in document (1), and, on the other hand, of the claimed N^{α}-Nsc-protected amino acids vis-à-vis the corresponding N^{α}-Fmoc-protected amino acids.

2.4.2 The Respondent did not deny that some of the known N^{α}-Nsc-protected amino acids **3** (cf. point 2.3 above) exhibited a stability comparable to that of the claimed N^{α}-Nsc-protected amino acids (cf. for instance, **3a**, **3g**, **3c**, **3b**, **3e**). He nevertheless argued that the stability of the range formed by the claimed N^{α}-Nsc-protected amino acids as a whole was better than the range formed by the N^{α}-Nsc-protected amino acids **3**.

However, such a comparison of ranges is unfair and does not meet a physical reality since the subject-matter of Claim 1 relates as does the prior document (1) to individual compounds, the stability of which individuals cannot be taken as a whole to form an artificial body.

Since the Respondent conceded that some of the N_{α}-Nsc-protected amino acids **3**, namely **3a**, **3b**, **3c**, **3e** and **3g**, exhibited the same or a better stability than the claimed N_{α}-Nsc-protected amino acids, an improvement in stability cannot be acknowledged to be successfully achieved.

2.4.3 Regarding the Respondent's comparison of the stability of the claimed N^{α}-Nsc-protected amino acids with that of

the corresponding N^{α}-Fmoc-protected amino acids reported in document (8), the Board points out that a comparison can only be fair and, thus, be taken into account when it is made vis-à-vis the closest prior art (Case law of the Boards of Appeal of the EPO, 4^{th} ed. 2001, I.D.7.7.2). However, document (1) is the closest state of the art and already describes N^{α}-Nsc-protected amino acids. Any comparison with the N^{α}-Fmoc-protected amino acids which are further away is, therefore, irrelevant and must be disregarded.

2.4.4 The Respondent, relying upon document (11), submitted further that the N^{α}-Nsc-protected amino acids His and Cys underwent less racemization than the corresponding Fmoc-protected amino acids in peptide synthesis. However, the same considerations and conclusions made above (under point 2.4.3) apply, since the N^{α}-Fmoc-protected amino acids do not represent the closest state of the art, but prior art being further away. Therefore, the Respondent's allegations cannot be taken into consideration.

2.4.5 Thus, in the absence of any technical effect successfully achieved vis-à-vis the closest state of the art, the technical problem to be solved starting from document (1) can only be seen in the provision of further N^{α}-protected amino acids useful for solid phase peptide synthesis.

2.5 As the solution to this problem, the patent in suit proposes N^{α}-Nsc-protected amino acids as defined in Claim 1 (cf. point II above).

2.6 The Board, in view of the examples Nos. 1, 2, 4, 5 and 6 is satisfied that the technical problem defined above is solved within the whole area claimed. The Appellant did not contest that finding.

2.7 It remains to be decided whether or not the proposed solution to the problem underlying the invention is obvious in view of the cited prior art.

2.7.1 Contrary to the Respondent's view, the teaching of document (1) is not limited to the individual N^{α}-Nsc-protected amino acids explicitly disclosed therein but teaches that the Nsc group in general may well be an appropriate temporary protection for α-amino groups in solid phase synthesis (cf. page 7821, second paragraph). That document teaches, in conclusion, that Nsc-protected amino acids appeared to be suitable intermediates for the solid phase peptide synthesis under conditions very similar to that used for Fmoc derivatives (cf. page 7824).

The relevant question is whether the person skilled in the art having studied the document (1) and being guided by the technical problem to be solved as defined in point 2.4.5 above would have been directed to select the N^{α}-Nsc-protected amino acids as defined in Claim 1 for performing solid phase synthesis. In that context, since the document (1) teaches that Nsc-protected amino acids appear to be suitable intermediates for the solid phase synthesis and discloses in that respect eight N^{α}-Nsc-protected amino acids deriving from naturally occurring N^{α}-amino acids, the presumption prevails that other N^{α}-Nsc-amino acids will exhibit the same valuable properties. It derives therefrom that the person

skilled in the art would have been directed with a reasonable expectation of success to design other N^{α}-Nsc-protected amino acids for solving the above defined technical problem thereby arriving without inventive ingenuity at the N^{α}-Nsc-protected amino acids of Claim 1.

2.7.2 The Respondent submitted, however, that the person skilled in the art was prevented from following that path since he would have expected in view of document (2) that at least some of the claimed N^{α}-Nsc-protected amino acids would be unstable.

The Board observes, first, that the N^{α}-Nsc-protected-D,L-Phe-OMe cited in document (2) is an ester, not the free acid as the compounds covered by the claimed invention, and cannot be considered as a deterrent in that respect. That would not have prevented the person skilled in the art from trying to design N^{α}-Nsc-protected amino acids other than those described in document (1), *inter alia* the claimed N^{α}-Nsc-protected amino acids.

The correct approach in assessing inventive step is not whether a skilled person would derive from given information in the prior art a certain predictability of success, as submitted by the Respondent, but rather whether it would be obvious to try something falling within the claims with a reasonable expectation of success, on the basis of the existing knowledge (cf. T 288/98, point 2.10 of the reasons).

2.7.3 The Respondent relying upon document (7) argued further that the production in good yields and high purity of the N^{α}-Nsc-protected amino acids of Claim 1 could not be

achieved by the methods described in document (1). Such methods, applied to amino acids which the claimed N^{α}-Nsc-protected amino acids derived from, did not yield industrial products. The claimed methods were the first to achieve this and did so in an inventive manner rendering the resulting N^{α}-Nsc-protected amino acids *per se* inventive. The decision T 595/90 (loc.cit.) was cited in that respect.

This decision specifies three independent criteria to be satisfied, the first being that there is no known way or applicable method in the art to make the product (reasons of the decision point 5, last paragraph). Therefore, the issue of whether or not a product results from an inventive process arises only in case there is **no applicable methods** to make it. Clearly, this is not the case here in view of the results set out in the Respondent's declaration (7) and the Respondent's submissions dated 23 August 2004, page 4, paragraph 3, stating that all claimed N^{α}-Nsc-protected amino acids are obtainable by performing either the Bolin method or the Schotten-Baumann reaction both methods being disclosed in document (1), even though the yield may be low in the particular case of the amino acids asparagine and glutamine.

2.7.4 To summarise, since the person skilled in the art was provided from document (1) with appropriate information pointing him in the direction of the claimed N^{α}-Nsc-protected amino acids to solve the above technical problem with a reasonable expectation of success (cf. point 2.7.1 above), the subject-matter of Claim 1 of either the main request or the first auxiliary request lacks inventive step.

Since the Board can only decide on a request as a whole, the main and first auxiliary requests must fail.

Second and third auxiliary requests

3. *Article 56 EPC - Inventive step*

3.1 Claim 1 of the second auxiliary request was limited to those N^{α}-Nsc-protected amino acids wherein R_2 is carboxamido-methyl, 2-carboxamidoethyl, N-xanthyl-carboxamidomethyl or 2-(N-xanthylcarboxamido)ethyl. Claim 1 of the third auxiliary request was limited to the N^{α}-Nsc-protected amino acids wherein R_2 is S-(triphenylmethyl)thiomethyl, 1-(triphenylmethyl)imidazolyl-4-methyl or S-(acetamidomethyl)thiomethyl". These N^{α}-Nsc-protected amino acids were also comprised in Claim 1 of the main and first auxiliary request.

3.2 In view of the findings set out above regarding Claim 1 of the main and first auxiliary request, the assessment of inventive step of the second and third auxiliary request is identical to that of the former requests since no further arguments other than those already submitted were put forward in that respect. The considerations given above for the main and first auxiliary request on the obviousness apply also to the individual N^{α}-Nsc-protected-amino acids as defined in Claim 1 of the second and third auxiliary request and result in the same conclusion that the subject-matter of Claim 1 of these auxiliary requests lacks inventive step (cf. point 2.7.4 above).

3.3 In these circumstances, the Respondent's second and third auxiliary request must also be rejected.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin R. Freimuth