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D E C I S I O N
of 31 May 2001

Case Number: T 0429/96 - 3.3.4

Application Number: 86900423.4

Publication Number: 0205555

IPC: C07K 7/10

Language of the proceedings: EN

Title of invention:
SERINE PROTEASE INHIBITORS AND METHODS FOR ISOLATION OF SAME

Patentee:
Amgen Inc.

Opponent:
Teijin Limited

Headword:
Serine protease inhibitors/AMGEN

Relevant legal provisions:
EPC Art. 83, 54, 56

Keyword:
"Admissibility of the grounds of opposition under Article 83 and 56 (yes)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive steps (yes)"

Decisions cited:
T 0737/90, T 0301/87

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0429/96 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 31 May 2001

Appellant: (Proprietor of the patent)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 5 March 1996 revoking European patent No. 0 205 555 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: L. Galligani
Members: R. E. Gramaglia
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal is against the decision of the opposition division revoking European patent No 0 205 555 (application No. 86 900 423.4 published as WO 86/03497) which had been opposed on grounds of Articles 100(a) EPC (lack of novelty and lack of inventive step) and 100(b) EPC (lack of sufficient disclosure). The patent had been granted on the basis of 26 claims for the non-AT designated Contracting States and 31 claims for AT. Claims 1 and 9 as granted for the designated Contracting States except AT read as follows:

"1. A purified serine protease inhibitor protein consisting of a single unfragmented polypeptide chain, said inhibitor being capable of inhibiting the protease activity of at least one serine protease and being in excess of 40% homologous to a native serine protease inhibitor isolated from parotid secretions.

9. A purified serine protease inhibitor consisting of a single unfragmented polypeptide chain, said serine protease inhibitor inhibiting the protease activity of at least one serine protease and comprising the amino acid sequence:

R_1-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-
Pro-Lys-Lys-Ser-Ala-Gln-Cys-Leu-R_2-Tyr-Lys-
Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-
Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-
Ile-Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-
Pro-Thr-Arg-Arg-Lys-Pro-Gly-Lys-Cys-Pro-Val-
Thr-Tyr-Gly-Gln-Cys-R_8-R_3-R_9-Asn-Pro-Pro-
Asn-Phe-Cys-Glu-R_4-Asp-Gly-Gln-Cys-Lys-Arg-
Asp-Leu-Lys-Cys-Cys-R_5-Gly-R6-Cys-Gly-Lys-

Ser-Cys-Val-Ser-Pro-Val-Lys-R_7,

wherein,

R_1 and R_7 are the same or different and are selected from the group consisting of amino acid residues; and R_2, R_3, R_4, R_5, R_6, R_8 and R_9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine."

II. The reason given for the refusal was that the subject-matter of claim 1 of all requests then on file lacked novelty. The opposition division also expressed in points 4 and 5 of the decision under appeal a negative provisional opinion about the issues of inventive step and sufficiency of disclosure of the claimed subject-matter.

III. The following documents are referred to in the present decision:

(1) Fritz H. in "Protein Degradation in Health and Disease", Ciba Foundation Symposium 75 (new series), Excerpta Medica, Amsterdam, Oxford, New York, pages 351-379 (1980);

(2) Ohlsson M. et al., Hoppe-Seyler's Z. Physiol. Chem., Vol. 364, pages 1323-1328 (1983);

(3) Ohlsson K. et al., Hoppe-Seyler's Z. Physiol. Chem., Vol. 358, pages 583-589 (1977);

(4) Kueppers F., Biochim. Biophys. Acta, Vol. 229, pages 845-849 (1971);

(5) Wallner O. et al., Hoppe-Seyler's Z. Physiol. Chem., Vol. 355, pages 709-715 (1974);

(6) Schiessler H. et al., Hoppe-Seyler's Z. Physiol. Chem. Vol. 357, pages 1251-1260 (1976);

(7) Seemüller U. et al., FEBS Letters, Vol. 199(1), pages 43-48 (April 1986);

(8) Fritz H., Biol. Chem. Hoppe-Seyler, Vol. 369, Suppl., pages 79-82 (1988).

IV. The board issued a communication pursuant to Article 11(2) of the rules of procedure before the Boards of Appeal expressing its provisional opinion.

V. Oral proceedings were held on 31 May 2001, during which the appellant (patentee) filed a new main request (claims 1 to 14 for the non-AT Contracting States and claims 1 to 17 for the Contracting State AT) in replacement of any preceding claim request, of which claim 1 for the non-AT Contracting States read as follows:

"1. A purified serine protease inhibitor consisting of a single unfragmented polypeptide chain, said serine protease inhibitor inhibiting the protease activity of at least one serine protease and comprising the amino acid sequence:

Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-
Pro-Lys-Lys-Ser-Ala-Gln-Cys-Leu-Arg-Tyr-Lys-
Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-
Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-
Ile-Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-
Pro-Thr-Arg-Arg-Lys-Pro-Gly-Lys-Cys-Pro-Val-

Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-Pro-
Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-
Asp-Leu-Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-
Ser-Cys-Val-Ser-Pro-Val-Lys-Ala."

Claim 2 was identical with claim 9 as granted. Claims 3 to 11 related to specific embodiments of the serine protease inhibitor of claim 2, while claims 12 to 14 covered pharmaceutical compositions and the first/further medical use of the serine protease inhibitor of claims 1 to 11.

Claims 1 to 14 for AT were identical to claims 1 to 14 for the non-AT States.

Claims 15 and 16 for AT read as follows:

"15. A process for preparing a serine protease inhibitor, consisting of a single unfragmented polypeptide chain, said serine protease inhibitor inhibiting the protease activity of at least one serine protease and comprising the amino acid sequence:

R_1-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-
Pro-Lys-Lys-Ser-Ala-Gln-Cys-Leu-R_2-Tyr-Lys-
Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-
Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-
Ile-Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-
Pro-Thr-Arg-Arg-Lys-Pro-Gly-Lys-Cys-Pro-Val-
Thr-Tyr-Gly-Gln-Cys-R_8-R_3-R_9-Asn-Pro-Pro-
Asn-Phe-Cys-Glu-R_4-Asp-Gly-Gln-Cys-Lys-Arg-
Asp-Leu-Lys-Cys-Cys-R_5-Gly-R6-Cys-Gly-Lys-
Ser-Cys-Val-Ser-Pro-Val-Lys-R_7,

wherein,

R_1 and R_7 are the same or different and are selected from the group consisting of amino acid residues; and R_2, R_3, R_4, R_5, R_6, R_8 and R_9 are the same or different and are selected from the group consisting of methionine, valine, alanine, phenylalanine, tyrosine, tryptophan, lysine, glycine and arginine, comprising the steps of:

(a) collecting mammalian parotid secretions;

(b) isolating the inhibitor from the parotid secretions by fractionating the proteinaceous material in the secretions;

(c) identifying the fractions which possess serine protease inhibiting activity, and

(d) concentrating the fractions which possess serine protease inhibiting activity.

16. A process for preparing a serine protease inhibitor, consisting of a single unfragmented polypeptide chain, said serine protease inhibitor inhibiting the protease activity of at least one serine protease and comprising the amino acid sequence:

Ser-Gly-Lys-Ser-Phe-Lys-Ala-Gly-Val-Cys-Pro-
Pro-Lys-Lys-Ser-Ala-Gln-Cys-Leu-Arg-Tyr-Lys-
Lys-Pro-Glu-Cys-Gln-Ser-Asp-Trp-Gln-Cys-Pro-
Gly-Lys-Lys-Arg-Cys-Cys-Pro-Asp-Thr-Cys-Gly-
Ile-Lys-Cys-Leu-Asp-Pro-Val-Asp-Thr-Pro-Asn-
Pro-Thr-Arg-Arg-Lys-Pro-Gly-Lys-Cys-Pro-Val-
Thr-Tyr-Gly-Gln-Cys-Leu-Met-Leu-Asn-Pro-Pro-
Asn-Phe-Cys-Glu-Met-Asp-Gly-Gln-Cys-Lys-Arg-
Asp-Leu-Lys-Cys-Cys-Met-Gly-Met-Cys-Gly-Lys-
Ser-Cys-Val-Ser-Pro-Val-Lys-Ala

comprising the steps of:

(a) collecting mammalian parotid secretions;

(b) isolating the inhibitor from the parotid secretions by fractionating the proteinaceous material in the secretions;

(c) identifying the fractions which possess serine protease inhibiting activity, and

(d) concentrating the fractions which possess serine protease inhibiting activity."

Claim 17 for AT was directed to a process for preparing a pharmaceutical composition.

VI. The arguments by the appellant were essentially as follows:

Admissibility of the grounds of appeal under Articles 83 and 56 EPC.

- Point 5 of the notice of opposition recited: "The invention, at least so far as claimed in claims 7 and 20 to 22, does not involve an inventive step in view of the disclosure of documents 1 to 6". However, these claims no longer belonged to the claim request as finally on file and the above statement was insufficiently substantiated.

Sufficiency of disclosure (Article 83 EPC)

- Although claim 2 was very broad, the patent in suit gave examples of variants exhibiting specific

combinations of amino acid alterations (see page 8, lines 5-19). Though troublesome, selecting the variants with the desired activity did not involve undue burden because the patent in suit disclosed how to test these variants.

Novelty

- Before the priority date of the patent in suit, several publications (documents (1) to (6)) reported attempts to isolate and characterize protease inhibitors from a variety of source materials. However, only mixtures of degraded protein fragments could be obtained. The technique and source material disclosed by these documents afforded only a mixture of degraded fragments rather than the isolated polypeptide consisting of a single unfragmented polypeptide chain as claimed.

- Post-published documents (7) and (8) had to be disregarded for the purpose of assessing the novelty. When taken as expert opinion, they confirmed, if anything, that the prior art protein was always fragmented.

Inventive step

- Departing from document (1) as closest prior art, the problem to be solved was to identify and isolate the undegraded serine protease inhibitor. No document of the prior art suggested that this task would have been possible, let alone gave a hint as to how to achieve it.

VII. The arguments by the respondent were essentially as follows:

Admissibility of the grounds of appeal under Articles 83 and 56 EPC

- The patentee withdrew before the opposition division the inadmissibility objection (see Minutes of the Oral Proceedings, page 1, third paragraph). In form 2300.1, Section VI relating to the grounds of opposition, the boxes corresponding to Articles 56 and 83 EPC had been crossed. Therefore these grounds of opposition were still valid throughout the appeal stage.

Sufficiency of disclosure (Article 83 EPC)

- The substitution of one or more amino acid residues in the inhibitor to create analogs thereof was described on page 9, lines 12 and 14 of the patent in suit (page 14, lines 14 and 17 of the published application as filed) with reference to two unpublished U.S. patent applications. Since these applications were not available to the public at the filing date of the patent in suit (also because one application number was missing), the production of variants was not sufficiently disclosed.

- It would require undue burden for the skilled person to select, among the great many variants covered by claim 2, those exhibiting the required property of inhibiting at least one serine protease.

Novelty

- The claims at issue covered secretory leukocyte proteinase inhibitor (SLPI), human seminal inhibitor (HUSI-I), antileukoproteinase, the proteinase inhibitor in human tears, cervical mucus inhibitor (CUSI) and bronchial mucus inhibitor (BMI), which were different names for the same protein termed mucus proteinase inhibitor (MPI) in post-published document (8), taken as an expert opinion. HUSI-I and BMI (documents (1), (3) and (6)), antileukoproteinase (document (2)), CUSI (documents (5) and (6)) had already been obtained in pure form.

- According to page 361 of document (1), HUSI-I consisted of a single polypeptide chain of about 100 amino acid residues. The fact that an incorrect amino acid sequence might have been assigned to HUSI-I was irrelevant for the purpose of novelty since the statement in a claim of intrinsic parameters such as the correct amino acid sequence for an otherwise known protein did not render it novel.

- The subject-matter of claims 15 and 16 for the Contracting State AT lacked novelty over document (2) which disclosed all the steps (a) to (d) stated in these claims.

Inventive step

- Document (1) was concerned with early attempts to characterize the inhibitor HUSI-I, known to be present in human seminal plasma. The problem to be

solved was to further purify the inhibitor in order to provide additional information about the amino acid sequence. The skilled person could have easily done this and sequenced other fragments to arrive at the whole sequence, as done in Example 3 of the patent in suit, which was also concerned with the determination of the amino acid sequence of the purified inhibitor by sequencing the fragments thereof.

- As for the variants covered by claim 2, it was obvious to make alternatives to the protein of claim 1.

VIII. The appellant (patentee) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the claims filed during the oral proceedings in the two versions, one for AT and one for the other designated Contracting States.

The respondent (opponent) requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Admissibility of the grounds of opposition under Articles 83 and 56 EPC

2. In the notice of opposition (cf points 5 and 6), in addition to objection to novelty, objections were raised and substantiated by the respondent under Articles 56 and 83 EPC in respect of some particular

aspects of the invention. However, the patent as granted was attacked as a whole and its revocation was requested on grounds of Article 100(a)(b) EPC. This has led to the revocation of the patent by the opposition division and to the subsequent filing upon appeal of an amended claim request aimed at restoring patentability. The board finds that the said grounds of opposition were sufficently substantiated in the notice of opposition. They are thus valid throughout the opposition-appeal proceedings and have to be examined in respect of the amended claims now on file within the legal and factual framework of the present appeal.

Articles 123(2),(3) and 84 EPC

3. Claims 1 to 14 for the non-AT Contracting States are identical with the corresponding granted claims 19, 9 to 18 and 24 to 26 in that order, while claims 1 to 17 for the Contracting State AT are identical with the corresponding granted claims 19, 9 to 18, 24 to 28 and 31 in that order. The respondent does not raise any formal objections to the claims at issue and the board also sees none.

Sufficiency of disclosure (Article 83 EPC)

4. The respondent argues that the production of variants of the inhibitor of claim 1 is not sufficiently disclosed because in the description (page 14, lines 14 and 17 of the published application as filed) reference is made to two U.S. patent applications which were not available to the public at the **filing date** of the patent in suit (also because one application number was missing). In the respondent's opinion, these cross-referenced applications contained the necessary

information for the skilled person to substitute by recombinant DNA methods one or more amino acid residues in the inhibitor to create analogs thereof.

In the board's judgement, however, a document incorporated by reference into the text of a European patent application has rather to become available to the public at the latest on the **publication date** of this European patent application, in order to be taken into account for the purpose of Article 83 EPC (see decision T 737/90 of 9 September 1993, points 3 and 5 of the "Reasons"). This requirement is fulfilled by cross-referenced "U.S. Patent Application Serial No. 678 822 filed December 6, 1984" which can be easily established to be the priority document of the International patent application published as W0 86/03519 on 19 June 1986 that corresponds to the European patent No. 0 205 475 (application No. 8 5905 953.7, date of filing 4 December 1985) published on 30 December 1986, ie on the same day as the application underlying the patent in suit.

As for the other U.S. patent application, to which incomplete reference is made, the additional question is whether it was retrievable without undue effort on the basis of the information provided in the patent in suit (cf the rationale of decision T 737/90, supra; see point 5). It can easily be established on the basis of the whole information given, including the correlation with the other reference, that this is the second priority document of the quoted International patent application, namely the U.S. Patent Application Serial 803 471 filed on 2 December 1985, of Pradip K. Bandyopadhyay et al. with title "Recombinant methods for isolating serine proteases inhibitors and DNA

sequences useful for same".

Therefore, it must be concluded that the skilled person had access to the technical contents of both documents at the publication date of the application underlying the patent in suit via the easily retrievable WO 86/03519 (EP 0 205 475). This provides the necessary information enabling the substitution of one or more amino acid in the inhibitor to create analogs thereof. In view of these findings, the board is satisfied that the patent in suit enables the skilled person to arrive at analogs of the claimed serine protease inhibitor.

5. In the respondent's view, undue burden would be required for the skilled person to select, among the great many variants covered by claim 2, those exhibiting the required property of inhibiting at least one serine protease.

In spite of the considerable amount of theoretically possible variations of the amino acid sequence, in the board's opinion, there is still likely to be a strong structural similarity between all the variants covered by the present claim 2. This view is confirmed when considering the passage on page 8, lines 5 to 19 of the patent in suit, which gives examples of variants exhibiting specific combinations of amino acid alterations. Therefore, it can be seen that all the variants share a substantial number of amino acid residues. The situation here, where the claimed products are limited to those having a certain structural relationship to one another, and a testable narrowly defined activity, must be distinguished from a situation where either the structure or the activity is not defined in a disputed claim, so that it can be said that some substances which it would be desirable to

make fall within the claim, but the description gives no guidance as to how they can be made (cf decision T 301/87 (OJ EPO 1990, 335).

6. In conclusion, the requirements of Article 83 EPC are fulfilled.

Novelty

Document (1)

7. The respondent argues that the serine protease inhibitor of claim 1 lacks novelty over document (1), disclosing a preparation called HUSI-I made from human seminal plasma and having a strong affinity for granulocytic elastase and cathepsin G.

In the board's view, however, the HUSI-I preparation disclosed by document (1) is a heterogeneous (page 361, line 1: "several multiple forms") and degraded (page 361, line 3: "due partly to proteolytic degradation") preparation. This finding is confirmed by post-published document (8) taken as an expert opinion, wherein it is stated on page 80, right-hand column that "Proteolytic modification of MPI [another name for HUSI-I] occurred extensively by seminal plasma proteases". In fact, document (1) gives the amino acid sequence of two HUSI-I degradation products predominating in the mixture. Therefore, it must be concluded that the source material and the preparation method disclosed by document (1) do not enable the skilled person to arrive at an isolated undegraded inhibitor according to claim 1 at issue.

Document (2)

8. In the respondent's view, document (2) is also novelty-destroying for claim 1 at issue because it discloses an antileukoproteinase from saliva or parotid secretion which is identical to HUSI-I.

However, the board observes that the preparation of document (2) is highly impure since it comprises "several distinct protein bands" once subjected to agarose gel electrophoresis (see page 1326, bottom of left-hand column). The concentration of the inhibitors in this impure preparation is also too low to appear as distinct protein bands (see passage bridging left-hand and right-hand column on page 1326 and Figure 3b). There is therefore neither a teaching in this document as to how to arrive at the purified and undegraded protein of claim 1 at issue, nor any unambiguous evidence that antileukoproteinase is identical with this undegraded serine protease inhibitor. In view of this, the subject-matter of claim 1 is novel over document (2). As a further consequence, the board has to dismiss the respondent's contention that claims 15 and 16 for the Contracting State AT lack novelty over document (2), disclosing all the steps (a) to (d) stated in these claims. As seen above, there is no evidence before the board that the result of applying steps (a) to (d) to the starting material of document (2) is the purified, undegraded serine protease inhibitor of claim 1 at issue.

Document (3)

9. As for the bronchial mucus inhibitor (BMI) described in document (3), which the respondent also views as anticipating the claimed inhibitor, the board notes that it exhibits a N-terminal Tyr (page 586, bottom of

right-hand column), a 99 amino acid chain length (see Table on page 587), no Trp residue (ibidem) and 12 to 14 Cys residues (page 588, left-hand column), while the claimed inhibitor has a N-terminal Ser, a 107 amino acid chain length, one Trp moiety and 16 Cys residues. These discrepancies, especially the N-terminal Tyr moiety as opposed to the Ser residue, suggest that the protein of document (3) is degraded or is a different one. It is true that the polyacrylamide gel electrophoresis (see page 585, right-hand column, penultimate paragraph) shows only one band, however, the respondent does not dispute that electrophoresis takes place under reducing conditions, where the protein fragments are cross-linked through -S-S- bridges.

Document (4)

10. The inhibitor of trypsin and chymotrypsin disclosed in this document has a molecular weight between 3,000 and 6,500 (see the Summary). It is smaller than the claimed inhibitor of 12 kD (see patent in suit, page 4, line 23). Therefore, it cannot affect the novelty of the claimed inhibitor.

Documents (5) and (6)

11. These documents have as co-author the author of document (1) (Prof. H. Fritz) and pre-date this document by six and four years, respectively. They relate to early characterization attempts of HUSI-I and cervical mucus derived inhibitor (CUSI). They do not provide any more technical information than document (1), according to which these inhibitors are mixtures of fragments.

12. In conclusion, owing to the techniques and/or source material of the prior art, any attempt to isolate and characterize the protease inhibitors yields either a different and shorter inhibitor (document (4)) or merely mixtures of degraded protein fragments (documents (1) to (3), (5) and (6)), rather than an isolated polypeptide consisting of a single unfragmented polypeptide chain as required by claim 1 in suit. The provision of this unfragmented serine protease inhibitor is a true technical achievement conferring novelty on present claim 1. Therefore, the respondent's contention that claim 1 merely relates to the provision of a correct amino acid sequence for an otherwise known protein, does not convince the board. Since claims 2 to 14 for the non-AT Contracting States and claims 1 to 17 for the Contracting State AT all rely on the novel protein of claim 1, there is no need to consider their novelty separately from that of claim 1.

Inventive step

13. The parties consider document (1) as representing the closest prior art and the board agrees as well. Document (1) relates to the best attempt before the priority date of the patent in suit to isolate and characterize the inhibitor HUSI-I, known to be present in human seminal plasma and having a strong affinity for granulocytic elastase and cathepsin G. The disclosure of document (1), however, does not lead to an isolated serine protease inhibitor consisting of a single unfragmented polypeptide chain as required by claim 1 in suit because the "HUSI-I" disclosed therein is a heterogeneous and degraded preparation (see

point 7 supra). The board is satisfied that the patent in suit solves the problem of providing such an isolated serine protease inhibitor consisting of a single unfragmented polypeptide chain. It has thus to be established whether or not the claimed protein follows in an obvious way from the prior art. In the board's view, document (1) does not suggest that it is possible to identify and isolate the claimed "native" inhibitor, much less teaches a purification process that would yield that protein. Consequently, the subject-matter of claim 1 fulfils the requirements of Article 56 EPC. Since claims 2 to 14 for the non-AT Contracting States and claims 1 to 17 for the Contracting State AT all rely on the inventive inhibitor of claim 1, there is no need to consider their inventive step separately from that of claim 1.

14. The respondent argues that the skilled person could have easily further purified HUSI-I of document (1) and sequenced other fragments to arrive at the whole sequence stated in claim 1 at issue, as done in Example 3 of the patent in suit.

In the board's view, though, it has first to be noted that the problem to be solved by the subject-matter of claim 1 is not the provision of the amino acid sequence but of a native, undegraded serine protease inhibitor. No prior art discloses the measures to be taken (eg starting material, succession of process steps) by the skilled person for arriving at this molecule.

Even if it were assumed, for the sake of reasoning, that finding the complete amino acid sequence of HUSI-I was the final task aimed at, the board observes that the skilled person was faced with serious difficulties in reconstructing the actual protein because, as seen

above (point 7), the preparation of document (1) was a mixture of degraded multiple inhibitory active forms. Therefore, the skilled person had not only to sequence the fragments but also to find out to which HUSI-I active form each of the fragments belonged, an arduous, if not impossible, task.

Adaptation of description

15. No objections are raised by the respondent to the amendments to the description effected to bring it into line with the claims, exception made for the wording "purified forms of protease inhibitors" on page 4, lines 39 to 41 of the description, which, in the respondent's view, implies a false distinction vis-à-vis the prior art also disclosing "purified forms of protease inhibitors". As emphasized under point 12 above, however, this is not the case. Therefore, the board sees no objections in this respect.

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 maintain the patent on the basis of the claims filed during the oral proceedings in the two versions, one for AT and one for the other designated Contracting States, and description pages 4 to 8 as filed during the oral proceedings and pages 3 and 9 to 14 as granted.

The Registrar: The Chairman:

U. Bultmann L. Galligani