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Datasheet for the decision of 17 December 2024

Case Number:	T 2543/22 - 3.3.02
Application Number:	15773570.5
Publication Number:	3126373
IPC:	C07K7/06
Language of the proceedings:	EN

Title of invention:
METHOD FOR PREPARING AMG 416

Patent Proprietor:
Amgen Inc.

Opponent:
COPA Copenhagen Patents K/S

Headword:
AMGEN / AMG 416

Relevant legal provisions:
EPC Art. 100(c), 100(a), 56

Keyword:
Grounds for opposition - added subject-matter (no)
Inventive step - (yes)

Decisions cited:

Catchword:

Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 2543/22 - 3.3.02

DECISION
of Technical Board of Appeal 3.3.02
of 17 December 2024

Appellant: (Opponent)	COPA Copenhagen Patents K/S Rosenørns Allé 1, 2. sal 1970 Frederiksberg C (DK)
Representative:	COPA Copenhagen Patents Rosenørns Allé 1, 2nd floor 1970 Frederiksberg C (DK)
Respondent: (Patent Proprietor)	Amgen Inc. One Amgen Center Drive Thousand Oaks, California 91320 (US)
Representative:	Page, Richard Mark Donald df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 11 October 2022 rejecting the opposition filed against European patent No. 3126373 pursuant to Article 101(2) EPC.**

Composition of the Board:

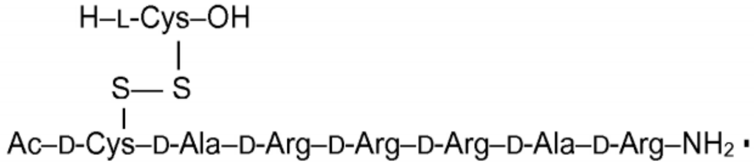
Chairman	M. O. Müller
Members:	M. Maremonti
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the opponent (appellant) lies from the decision of the opposition division to reject the opposition against European patent No. 3 126 373 ("the patent").

II. Claim 1 as granted reads as follows:

"*1. A method for preparing AMG 416 as set forth in formula (I):*



$$\begin{array}{l} \qquad\qquad \text{H–L-Cys–OH} \\ \qquad\qquad\qquad | \\ \qquad\qquad\ \text{S—S} \\ \qquad\qquad\ | \\ \text{Ac–D-Cys–D-Ala–D-Arg–D-Arg–D-Arg–D-Ala–D-Arg–NH}_2 . \end{array}$$

said method comprising:

contacting a peptide having the structure of Ac-D-Cys(SPy)-D-Ala-D-Arg-D-Arg-D-Arg-D-Ala-D-Arg-NH_2 *(SEQ ID NO:4) with L-Cys to produce a conjugated product of formula (I)*".

III. The opposition was based on the grounds under Article 100(c) EPC and Article 100(a) in combination with Article 56 EPC. Reference was made, *inter alia,* to the following documents:

D1: WO 2011/014707 A2

D2: Andreu *et al.*, "*Formation of Disulfide Bonds in Synthetic Peptides and Proteins*", Chapter 7 in: Methods in Molecular Biology, vol. 35, Peptide Synthesis Protocols, edited by M. W. Pennington and B. M. Dunn, Humana Press Inc., Totowa, NJ, 1994, pages 91-169

D3: Hermanson (ed.): Bioconjugate Techniques (third edition), Academic Press, 2013, ISBN 978-0-12-382239-0, pages 242-4 and 681-5

D4: Castell and Tun-Kyi, "*The Removal of S-Cysteine Protection by Means of 2-Pyridine Sulfenyl Chloride and the Subsequent Formation of Disulfide Bonds*", Helvetica Chimica Acta, vol. 62, fasc. 7, No. 253, 1979, pages 2507-10

D5: Nagata *et al.*, "*Bombyxin-H and Its Disulfide Bond Isomers: Synthesis and Activity*", Peptides, vol. 13, 1992, pages 653-62

D6: Causton and Sherman, "*A comparison of three- and four-helix bundle TASP molecules*", J. Peptide Science, 8, 2002, pages 275-82

D7: Hossain *et al*, "*Regioselective Disulfide Solid Phase Synthesis, Chemical Characterization and In Vitro Receptor Binding Activity of Equine Relaxin*", International Journal of Peptide Research and Therapeutics, vol. 12, No. 3, 2006, pages 211-5

D8: Baumhover *et al*, "*Synthesis and In Vitro Testing of New Potent Polyacridine-Melittin Gene Delivery Peptides*", Bioconjugate Chem., 21, 2010, pages 74-83

D9: Hossain *et al*, "*Synthesis, Conformation, and Activity of Human Insulin-Like Peptide 5 (INSL5)*", ChemBioChem 9, 2008, pages 1816-22

D10: Hossain *et al.*, "*Use of a Temporary "Solubilizing" Peptide Tag for the Fmoc Solid-Phase Synthesis of Human Insulin Glargine via Use of Regioselective Disulfide Bond Formation*", Bioconjugate Chem. 20, 2009, pages 1390-6

D11: Kwak *et al.*, "*Solid Phase Synthesis of an Analogue of Insulin, A0:R glargine, That Exhibits Decreased Mitogenic Activity*", Int. J. Pept. Res. Ther., 2010, 16:153-8

D12: Schulz *et al.*, "*Preparation of Disulfide-Bonded Polypeptide Heterodimers by Titration of Thio-Activated Peptides with Thiol-Containing Peptides*", Tetrahedron 56, 2000, pages 3889-91

D13: Ghosh and Fan, "*A novel method for sequence independent incorporation of activated/protected cysteine in Fmoc solid phase peptide synthesis*", Tetrahedron Letters 41, 2000, pages 165-8

D14: Maruyama *et al.*, "*2,2'-Bispyridyl disulfide rapidly induces intramolecular disulfide bonds in peptides*", Peptides 20, 1999, pages 881-4

D15: Fletcher and Hughes, "*A novel approach to the regioselective synthesis of a disulfide-linked heterodimeric bicyclic peptide mimetic of brain-derived neurotrophic factor*", Tetrahedron Letters 45, 2004, pages 6999-7001

D16: Ruiz-Gayo *et al.*, "*Uteroglobin-like peptide cavities I. Synthesis of antiparallel and parallel dimers of bis-cysteine peptides*", Tetrahedron Letters, vol. 29, No. 31, 1988, pages 3845-8

D17: WO 98/12217

D24: Excerpts from the AMGEN Manufacturing Process Development for AMG 416, an excerpt from the marketing authorisation application (MAA) filing in Europe dated 2 September 2015

D25: Excerpts from an AMGEN internal report on the development of the claimed method for preparing AMG 416, dated 23 September 2013

IV. The opposition division came, *inter alia*, to the following conclusions:

- None of the grounds for opposition invoked by the appellant prejudiced maintenance of the patent as granted.
- In particular, the claimed subject-matter involved an inventive step in view of D1 taken as the closest prior art.

V. In the statement of grounds of appeal and a subsequent letter, the appellant contested the opposition division's reasoning and argued, *inter alia*, that the subject-matter of independent claims 1 and 6 as granted lacked an inventive step. Additionally, the subject-matter of granted claim 2 extended beyond the content of the application as filed.

VI. In its reply to the appeal and a subsequent letter, the patent proprietor (respondent) rebutted the appellant's arguments, arguing, *inter alia*, that the grounds for opposition under Article 100(a) and (c) EPC did not prejudice maintenance of the patent as granted.

VII. The parties were summoned to oral proceedings as per their requests. In preparation for the oral proceedings, the board issued a communication under Article 15(1) RPBA.

VIII. Oral proceedings before the board were held by videoconference on 17 December 2024 in the presence of both parties.

IX. Final requests relevant to the decision

The appellant requested that the appealed decision be set aside and that the patent be revoked in its entirety.

The respondent requested that the appeal be dismissed, implying that the patent be maintained as granted.

X. As regards the parties' submissions that are relevant to the decision, reference is made to them in the reasons for the decision below.

Reasons for the Decision

Main request - patent as granted - claim 2 - ground for opposition under Article 100(c) EPC - added subject-matter

1. Claim 2 as granted reads as follows, the amendments to claim 5 of the application as filed having been highlighted by the board:

"~~5~~***2****. The method of claim* ***1*** ~~*4*~~*, wherein* ***said contacting comprises dissolving*** *the peptide* ~~*is contacted with*~~ ***in*** *an aqueous solution comprising L-Cys and trifluoroacetic acid* ***(TFA)***".

For the application as filed, reference is made to the application as published.

1.1 The appellant submitted that the step of "*dissolving*" the peptide in an aqueous solution of L-cysteine (L-Cys) and TFA was not directly and unambiguously disclosed in the application as filed. Claim 5 as filed merely disclosed contacting the peptide with such a solution, but no dissolution was mentioned. According to paragraph [0020] of the application as filed, the peptide was not dissolved in an aqueous solution comprising L-Cys and TFA, but first dissolved in an isopropyl alcohol-water solution, which was then mixed with an aqueous solution comprising L-Cys. Alternatively, paragraph [0096] of the application as filed had been referred to by the opposition division (appealed decision, point 2.3 on page 3). However, the appellant argued that this paragraph was part of example 3, disclosing a method comprising more details than those specified in claim 2 as granted. Moreover, this paragraph disclosed first dissolving the peptide in 0.2% TFA solution, and afterwards adding L-Cys. The subject-matter of granted claim 2 thus amounted to an impermissible intermediate generalisation of example 3 of the application as filed.

1.2 The board disagrees, and concurs with the respondent that the basis for the subject-matter of granted claim 2 is found in claims 4 and 5 as filed.

In fact, claim 4 as filed corresponds to claim 1 as granted (point II above) and requires that the peptide having the structure Ac-D-Cys(SPy)-D-Ala-D-Arg-D-Arg-D-Arg-D-Ala-D-Arg-NH_2 (referred to hereinafter as the "SPy-intermediate") be contacted with L-Cys to produce the conjugated product AMG 416.

Claim 5 as filed, dependent from claim 4, specifies that the SPy-intermediate is contacted with an aqueous solution of L-Cys and TFA. In order to form the conjugated product AMG 416 as required by claim 4 as filed, the SPy-intermediate must dissolve in the aqueous solution of L-Cys and TFA, with which it is contacted. Otherwise, no conjugation of the SPy-intermediate with L-Cys would take place. It is noted that at the oral proceedings the appellant did not dispute that the SPy-intermediate is soluble in an aqueous solution.

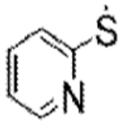
1.3 For these reasons, the board concludes that the combination of claims 4 and 5 as filed directly and unambiguously discloses the subject-matter of claim 2 as granted.

1.4 Therefore the ground for opposition under Article 100(c) EPC does not prejudice maintenance of the patent as granted.

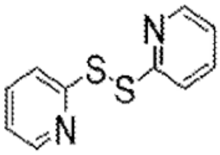
Main request - patent as granted - claim 1 - ground for opposition under Article 100(a) EPC - inventive step under Article 56 EPC

2. Invention

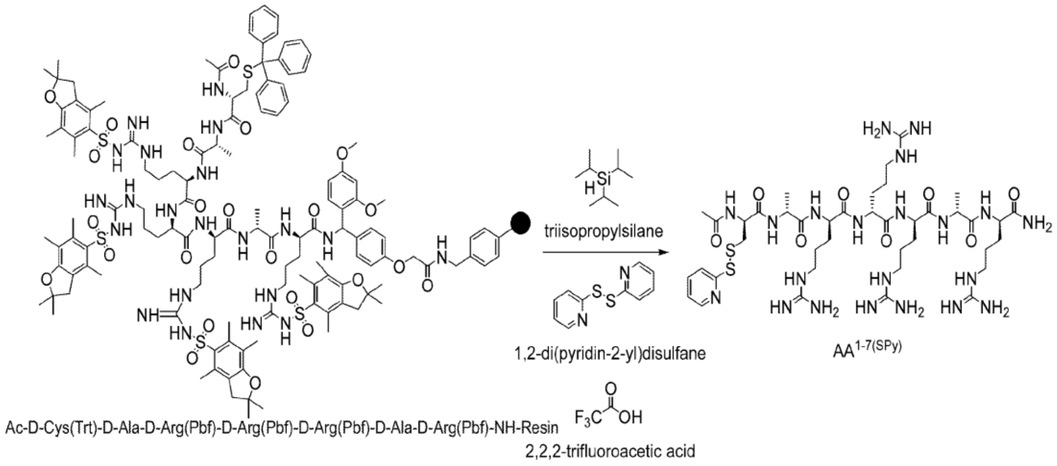
2.1 As mentioned above, the peptide required by claim 1 as granted (point II above) to conjugate with L-Cys to produce AMG 416 is referred to as the SPy-intermediate, where "SPy" represents 2-pyridinesulfenyl, having the following structure:



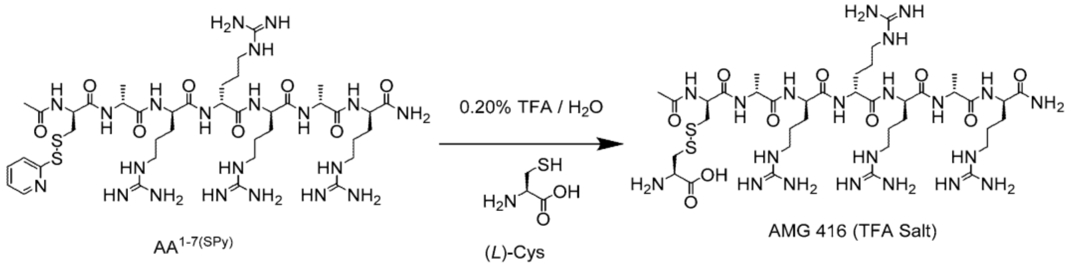
2.2 According to the patent (see paragraphs [0056] to [0060]), the SPy-intermediate is obtained by first assembling the main chain linear fragment of AMG 416 by using a standard solid-phase protocol employing Fmoc-protection strategy and a Rink amide resin, and then cleaving this linear fragment from the resin by using, *inter alia*, dipyridyl disulfide (DPDS). DPDS has the following structure:



This procedure is shown in figure 3 of the patent, which is reproduced below, where $AA^{1-7(SPy)}$ is the SPy-intermediate as defined in granted claim 1:



2.3 The subsequent conjugation of the obtained SPy-intermediate with L-Cys as required by claim 1 as granted is shown in figure 4 of the patent, reproduced below:



3. Closest prior art

3.1 In accordance with the appealed decision (page 7, point 3.3), both parties indicated document D1 as the closest prior art.

3.2 D1 (paragraphs [0003] and [0014]) concerns compounds of the general formula X_1-X_2-X_3-X_4-X_5-X_6-X_7 stated to have activity to decrease parathyroid hormone levels. Among a large number of specific compounds, D1 discloses (paragraphs [0030] to [0033], [0117], [0140] and claims

20 to 23) AMG 416 as defined in granted claim 1, identified in D1 as Ac-c(C)arrar-NH_2 (SEQ ID NO:3), i.e. bearing at the N-terminal position X_1 a D-Cys conjugated to an L-Cys by a disulfide bond.

3.3 According to paragraph [0242] of D1, peptides and conjugates are prepared by solid-phase chemistry using sequential coupling of Fmoc-amino acids to Rink-amide resin. The assembled peptide is cleaved from the resin with a TFA cocktail, isolated by precipitation with diethyl ether, purified by HPLC and isolated in the TFA salt form.

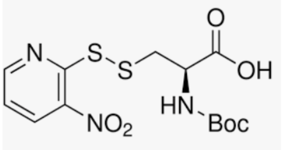
4. Distinguishing feature

It is common ground that the subject-matter of claim 1 as granted differs from the above-mentioned disclosure in D1 in that the unprotected SPy-intermediate is contacted with unprotected L-Cys to produce AMG 416. In fact, besides the above-mentioned general disclosure in paragraph [0242], D1 does not give any further detail as regards the steps followed to produce the disclosed compounds, let alone AMG 416. In particular, D1 does not disclose how the disulfide bond connecting D-Cys of the linear peptide to L-Cys is realised (see structure of AMG 416 in claim 1 as granted, point II above).

5. Objective technical problem

5.1 The appellant submitted that no comparison of the claimed method with the method taught in D1 had been provided. It contested the opposition division's reasoning, especially that it could be derived from the examples of the patent that the claimed method was suitable for scale-up (appealed decision, page 8). It argued that claim 1 as granted defined a method comprising a single step and did not make any reference to the scale of the method. The other technical effects alleged by the respondent, i.e. a reduction in the steps needed to produce AMG 416 or a cost efficiency of the claimed method, could not be accepted either, since granted claim 1 did not specify how the peptide was synthesised, purified, converted into the SPy-intermediate and conjugated with L-Cys so as to obtain AMG 416. Post-published evidence D24 and internal report D25 could not support any technical effect of the distinguishing feature either. Both D24 and D25 disclosed a far more specific method for producing AMG 416, comprising several steps, which were all absent from granted claim 1. Therefore these documents could not be used to support technical effects achieved across the whole scope claimed. Hence the appellant concluded that no technical effect could be derived from the above-mentioned distinguishing feature.

5.2 Additionally, the appellant argued that it was doubtful that the skilled person would have inferred from paragraph [0242] of D1 that AMG 416 was entirely produced by solid-phase synthesis. The appellant referred to paragraph [0005] of the patent, acknowledging the disclosure of D1. According to this paragraph, AMG 416 was produced in D1 by solid-phase synthesis of the Fmoc-protected D-amino acids, cleavage of this material from the resin and formation of the disulfide bond by reacting the cleaved material with Boc-L-Cys(NPyS)-OH, i.e. protected L-Cys. The structure of such Boc-L-Cys(NPyS)-OH is reproduced below:



5.3 Hence the appellant stated that, on the basis of the sole disclosure in paragraph [0242] of D1, the way in which AMG 416 was synthesised was left open, so that, in the absence of any technical effect, the objective technical problem had to be formulated as the provision of a suitable way of forming the disulfide bond of AMG 416. Alternatively, on the basis of the above-mentioned more detailed disclosure in paragraph [0005] of the patent, the objective technical problem was the provision of an alternative way of forming the disulfide bond of AMG 416.

5.4 The board holds that the objective technical problem has to be formulated in the light of the technical effect(s), if any, associated with the feature(s) distinguishing the claimed subject-matter from the disclosure in D1 as the closest prior art. Statements in the patent, *inter alia*, in paragraph [0005], should remain unconsidered. The above-mentioned disclosure in paragraph [0242] of D1 makes it clear that peptides and conjugates of D1, and thus also AMG 416, are synthesised by solid-phase chemistry and that the assembled peptides are cleaved from the resin. The board thus concurs with the respondent that the assembly of the entire peptide occurs in D1 in the solid phase. The doubts expressed by the appellant were not corroborated by any evidence and thus amount to mere speculation.

5.5 The respondent referred to several advantages deriving from the above-mentioned distinguishing feature. However, the board assumes, for the sake of argument only and in the appellant's favour, that no technical effect is associated with the above-mentioned distinguishing feature. Given this assumption, starting from the disclosure in paragraph [0242] of D1 (see above), the objective technical problem has to be seen as the provision of an alternative way to produce AMG 416.

6. Obviousness of the claimed solution

The appellant referred to common general knowledge and any of documents D4 to D17 to be combined with D1 for its arguments on obviousness. The arguments can be summarised as follows.

6.1 Common general knowledge

6.1.1 D2 represented the common general knowledge as regards the formation of disulfide bonds in peptides. Various techniques for forming disulfide bonds were disclosed, *inter alia*, on pages 116 and 117 of D2. Among the various techniques mentioned, D2 disclosed that one way to activate peptides containing cysteine in the free thiol form directly, both in solution and on the solid phase, was by application of DPDS. This was the same reagent used in the patent. Therefore it was obvious to activate the D-Cys residue in the X_1 position of the peptide disclosed in paragraph [0030] of D1 with DPDS and subsequently conjugate the obtained SPy intermediate with an L-Cys residue as required by claim 1 as granted. It was conceded that this technique of forming disulfide bonds was described on page 116 of D2 as having advantages but also disadvantages. However, the same was true for the other techniques disclosed in D2, see page 117. No technique was described in D2 as being exclusively beneficial or preferred.

6.1.2 D3 was also representative of the common general knowledge, and disclosed techniques for forming bioconjugates. According to page 243, pyridyl disulfides were the most popular type of thiol-disulfide functional groups highly efficient to undergo interchange reactions with sulfhydryl-containing molecules to yield a single disulfide product. Hence the skilled person would have activated the D-Cys residue in the X_1 position of the peptide disclosed in paragraph [0030] of D1 with DPDS before conjugating the same to an L-Cys residue.

6.1.3 Therefore the skilled person would have had a more than reasonable expectation of success that, by using the commonly known SPy route (i.e. by using DPDS) for the disulfide bond formation, AMG 416 would have been produced. This view was also confirmed by post-published document D24 and internal report D25, according to which the DPDS route was a standard one and represented the first choice made to synthesise AMG 416.

6.1.4 Therefore it had to be concluded that, starting from D1, the subject-matter of claim 1 was obvious in view of common general knowledge.

6.2 Documents D4 to D17

6.2.1 Additionally, the appellant submitted that each of D4 to D17 disclosed the disulfide bond formation via the SPy route required by granted claim 1. SPy intermediates of various peptides were successfully formed, ranging from short peptides (e.g. D4), heptapeptides as the SPy-intermediate of granted claim 1 (e.g. D16), to longer peptides (e.g. D5, D7), which were then conjugated with L-Cys.

6.2.2 As an example, the appellant referred to D4, which disclosed 2-pyridine sulfenyl chloride as a useful reagent for simultaneously deprotecting and activating the mercapto group of cysteine and cysteine peptides prior to the disulfide bond formation (see summary and reaction scheme on page 2508). According to D4, 2-pyridine sulfenyl chloride offered the unique advantage of simultaneous deprotection and activation of SH groups, thus enabling a facile disulfide bond formation with another SH group (see page 2509, first paragraph). This helped eliminate several steps during synthesis, using this specific active intermediate for forming disulfide bonds. Moreover, D4 described that deprotection, activation and disulfide bond formation by means of 2-pyridine sulfenyl chloride left other protecting groups like BOC intact. Therefore the skilled person would have used the approach of D4 to activate the D-Cys residue in the thiol-containing residue in the X_1 position of the peptide of D1 before conjugating the same to the L-Cys residue, as required by granted claim 1.

6.2.3 Another example was D13, disclosing that the activation of Cys with DPDS could be performed simultaneously with cleavage of the peptide backbone from the resin. D13, like the patent, addressed the activation of a cysteine residue at the N-terminal end of a short peptide, see page 166, scheme 1, sequences 2 and 3. D13 taught assembling the peptide on a resin, and cleaving it from the resin while treating it with DPDS, as both reactions took place under the same acidic conditions, see page 166, first and second paragraphs. It was obvious to use this approach to eliminate an entire process step from the synthesis. D13 also suggested purifying the SPy peptide via HPLC, indicating its stability and suitability for industrial processing. For this reason alone, it was obvious, starting from D1, to provide the SPy-intermediate in solution and to activate the cysteine of the peptide backbone rather than the free cysteine.

6.2.4 Also, D14 confirmed in the introduction on page 881 that DPDS was a common reagent in peptide chemistry, especially for forming disulfide bonds. A successful example was described on page 883 of D14.

6.2.5 Another example was illustrated in D15, disclosing on page 7000 that Fmoc-Cys-(Acm) was treated with DPDS, yielding the SPy derivative of Fmoc-cysteine; in the same way as defined in granted claim 1, the purified activated SPy peptide was then coupled to a free cysteine to afford a heterodimeric adduct.

6.2.6 Further examples were disclosed in D5 to D12, D16 and D17.

6.2.7 The appellant thus concluded that the subject-matter of claim 1 as granted was obvious starting from D1 in view of the disclosure in each of D4 to D17.

6.3 These arguments are not persuasive. The board concurs with the respondent's view that the subject-matter of claim 1 as granted was not obvious to the skilled person, having regard to the documents invoked by the appellant, for the following reasons.

6.3.1 As submitted by the respondent, when starting from the above-mentioned general disclosure in paragraph [0242] of D1, and assuming that the skilled person would have known how to apply this disclosure to specifically produce AMG 416 (the disclosure in paragraph [0242] of D1 is not restricted to the preparation of AMG 416 but extends to numerous peptides different from AMG 416), several steps would still have been needed to arrive at the claimed method. In fact, the skilled person would at least have had to

- divert from the explicit teaching of D1 to perform the entire synthesis including the conjugation with L-Cys in the solid phase
- activate the D-Cys on the peptide backbone linked to the resin and not the L-Cys to be conjugated
- select the activation agent to be used, especially DPDS
- react the unprotected activated peptide backbone cleaved from the resin with unprotected L-Cys.

6.3.2 Common general knowledge

Document D2 generally reviews a number of methods suitable for forming disulfide bonds in peptides in both solid phase and in solution. Advantages and disadvantages of these various methods are identified. In particular, as pointed out by the respondent, besides DPDS, D2 discloses on pages 116 and 117 a variety of other aromatic sulfenyl halides for the formation of disulfide bonds, for example by using a 3-nitro-2-pyridine sulfenyl group (NPys). Besides activation of peptide backbones, both in solution and in solid phase, D2 suggests (sentence bridging pages 116 and 117) using Boc-Cys(NPyS)-OH, i.e. protected Cys, to incorporate Cys into synthetic peptides. Such a route could be performed either on the resin-bound peptide or on the peptide in solution. A SPy peptide is shown in scheme 5 on page 126 of D2, but referring to a structurally completely different peptide from the SPy-intermediate of granted claim 1. The claimed SPy-intermediate is not disclosed in D2, let alone its conjugation with unprotected L-Cys. Even assuming that in view of D2 the skilled person would have taken a route based on a SPy intermediate, D2 still contains no teaching as regards which cysteine has to be activated with DPDS and whether the formation of the disulfide bond should occur in solution or on the resin.

As regards D3, the board concurs with the respondent's view that this document shows the possibility in general of activating a thiol residue in bioconjugates. D3 refers (page 243, left-hand column) to pyridyl-dithiol-containing crosslinking and modification reagents stated to be highly efficient in forming disulfide bonds with sulfhydryl-containing molecules. D3 does not concern peptide synthesis. The focus of D3 is, rather, on the activation of resins to be used, for example, as chromatography supports, see page 681, right-hand column.

6.3.3 Documents D4 to D17

As regards documents D4 to D17, the board agrees with the respondent that these documents, while describing the use of DPDS to form SPy peptides, do not disclose the specific SPy-intermediate of granted claim 1, let alone its conjugation in unprotected form with unprotected L-Cys.

Document D4 describes the use of 2-pyridine sulfenyl chloride and DPDS for the preparation of a disulfide bond in a very specific peptide synthesis of a short peptide comprising only glycine and cysteine residues in both peptide chains (C and D), see page 2509, last step. Thus, although the same group (DPDS) is used for Cys activation, the peptide of D4 has a completely different structure from AMG 416. Moreover, no conjugation between a peptide chain and unprotected L-Cys is disclosed.

D5 concerns (pages 655 to 657 and figure 3) the synthesis of Bombyxin II, an insulin superfamily peptide. Like D4, D5 too discloses the use of DPDS for forming disulfide bonds in a very specific peptide synthesis. However, D5 does not mention the SPy-intermediate of granted claim 1, let alone its conjugation with unprotected L-Cys.

D6 also discloses (page 277 and figure 3) the use of DPDS for forming a disulfide bond between the Cys of a peptide and a template. However, as in the previous documents, the SPy-intermediate of granted claim 1 is not mentioned, let alone its conjugation with unprotected L-Cys.

D7 discloses (page 212) the use of DPDS to activate a Cys present in a first peptide chain. The activated SPy peptide chain is then connected to the Cys of a second peptide chain, thus forming a disulfide bond. Therefore, as in the previous documents, the SPy-intermediate of granted claim 1 is not mentioned, let alone its conjugation with unprotected L-Cys.

A teaching analogous to D7 is reported in all of documents D8 (pages 75 and 76), D9 (figure 4 and right-hand column on page 1820), D10 (page 1392, left-hand column, and figure 3), D11 (page 155, right-hand column), D12 (Scheme 1 and page 3891), D16 (pages 3845 and 3846, Scheme 2) and D17 (referring to D16 on page 22, lines 21 to 26), also disclosing the use of DPDS to activate a Cys present in a first peptide chain to then be connected via a disulfide bond to a second peptide chain. However, as in the previous documents, the SPy-intermediate of granted claim 1 is not mentioned, let alone its conjugation with unprotected L-Cys.

D13 discloses (pages 166 and 167 and Scheme 1) a method for activating the Cys present in various peptides having nine or ten amino acids by using either a nitropyridine sulfenyl (NPys) or a pyridine sulfenyl (Pys) activating group. The use of these groups allows the simultaneous cleavage of the peptides from the resin on which they were synthesised. However, D13 does not disclose any further reaction with another peptide, let alone with unprotected L-Cys to form a disulfide bond.

D14 discloses (pages 882 and 883, table 1 and figure 1) the formation of intramolecular disulfide bonds (i.e. within one peptide chain) in specific peptides by using DPDS. D14 does not disclose any reaction with another peptide/cysteine to form a disulfide bond. As in the previous documents, the SPy-intermediate of granted claim 1 is not mentioned, let alone its conjugation with unprotected L-Cys.

D15 describes (Scheme 2 on page 7000) the conjugation of an Fmoc-protected cysteine SPy intermediate, i.e. an Fmoc-protected cysteine that has been activated with DPDS, with a free Cys to form a Cys dimer. This model approach is then used in D15 to form a disulfide bond between two peptide chains so as to obtain bicyclic peptide (1), see Scheme 3 on page 7000.

6.4 From what is set out above, it is acknowledged that, on the basis of common general knowledge as represented by documents D2 and D3 or the teaching contained in all the documents D4 to D17, the skilled person would have regarded DPDS as a group known to be used to activate the Cys present in a peptide chain to subsequently form a disulfide bond with another Cys present in a second peptide chain.

However, as stated above, the use of DPDS is only one of various steps that the skilled person would have had to follow in order to arrive at the claimed subject-matter in a way alternative to D1. Its combination with all other necessary steps is not rendered obvious by the cited prior art. In other words, the above-mentioned common general knowledge or the teaching of D4 to D17 could have been combined with all the other necessary steps needed to arrive at the subject-matter of granted claim 1 only by using impermissible hindsight. Starting from D1, the skilled person would not have had a reasonable expectation of producing AMG 416 in an alternative way by the mere use of DPDS.

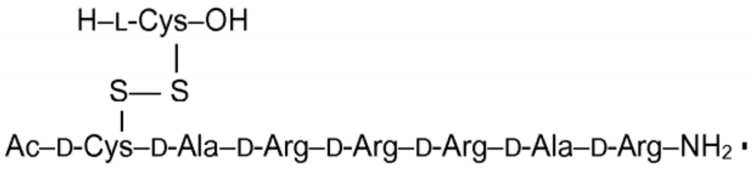
6.5 D24 and D25 were filed by the respondent to corroborate the presence of technical effects of the claimed method. However, D24 is post-published and D25 (internal report) is not prior art either. They concern the method disclosed in the patent and cannot be used as secondary documents to be combined with D1 to arrive at the claimed subject-matter. Therefore their content is irrelevant as regards the obviousness of the subject-matter of claim 1 as granted.

7. For these reasons, the board concludes that the subject-matter of claim 1 as granted involves an inventive step within the meaning of Article 56 EPC.

Main request - patent as granted - claim 6 - ground for opposition under Article 100(a) EPC - inventive step under Article 56 EPC

8. The appellant also raised inventive-step objections against the subject-matter of independent claim 6 as granted. Claim 6 as granted reads as follows:

"*6. A method for preparing AMG 416 as set forth in formula (I):*



$$\begin{array}{l} \qquad\qquad \text{H–L-Cys–OH} \\ \qquad\qquad\qquad | \\ \qquad\qquad \text{S—S} \\ \qquad\qquad | \\ \text{Ac–D-Cys–D-Ala–D-Arg–D-Arg–D-Arg–D-Ala–D-Arg–NH}_2\text{.} \end{array}$$

said method comprising:

purifying by HPLC a peptide having the structure Ac-D-Cys(SPy)-D-Ala-D-Arg-D-Arg-D-Arg-D-Ala-D-Arg-NH$_2$ *(SEQ ID NO:4) in a solution of trifluoroacetic acid (TFA); performing solvent exchange by azeotropic distillation on the purified peptide; and contacting the purified peptide with L-Cys to produce a conjugated product of formula (I).*"

8.1 In its communication issued under Article 15(1) RPBA in preparation for the oral proceedings, the board noted that claim 6 as granted includes all the features of granted claim 1 and is thus, *de facto*, dependent on claim 1 as granted. The appellant did not reply in writing to this observation by the board.

8.2 At the oral proceedings, the board maintained this opinion and stated that since the subject-matter of granted claim 1 had been found to involve an inventive step the same applied *mutatis mutandis* to the subject-matter of granted claim 6. The appellant did not wish to make any comment in this respect.

8.3 Therefore the board concludes that the subject-matter of claim 6 as granted involves an inventive step for the same reasons as for claim 1 as granted.

9. Since no other inventive-step objections were raised by the appellant, the board concludes that the ground for opposition under Article 100(a) EPC in combination with Article 56 EPC does not prejudice maintenance of the patent as granted.

Conclusions

10. None of the appellant's objections is convincing. Therefore the appeal against the opposition division's decision rejecting the opposition is not allowable and must be dismissed, implying that the patent is maintained as granted.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

Beschwerdekammern des Europäischen Patentamts ✦ Boards of Appeal of the European Patent Office ✦ Chambres de recours de l'Office européen des brevets

U. Bultmann M. O. Müller

Decision electronically authenticated