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Datasheet for the decision of 27 January 2021

Case Number: T 2635/16 - 3.3.02

Application Number: 09720914.2

Publication Number: 2262775

IPC: C07D231/12, A61K31/4155, A61P35/00, A61P37/00

Language of the proceedings: EN

Title of invention:

(E)-N-(2-AMINO-PHENYL)-3-{1-[4-(1-METHYL-1H-PYRAZOL-4-YL)-BENZENESULFONYL]-1H-PYRROL-3-YL}-ACRYLAMIDE SALTS

Applicant:

4SC AG

Headword:

Relevant legal provisions:

EPC Art. 123(2), 54, 56, 83

Keyword:

Amendments - allowable (yes)
Novelty - (yes): Selection from two lists one being present in a claim of the prior art document
Inventive step - (yes)

Decisions cited:
T 0012/81, G 0003/89, G 0001/03, G 0002/10, G 0001/16

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2635/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 27 January 2021

Appellant: (Applicant)	4SC AG Am Klopferspitz 19 a 82152 Planegg - Martinsried (DE)
Representative:	Kilger, Ute Boehmert & Boehmert Anwaltspartnerschaft mbB Pettenkoferstrasse 22 80336 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 12 July 2016 refusing European patent application No. 09720914.2 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	P. de Heij

Summary of Facts and Submissions

I. The appeal of the applicant (hereinafter: appellant) lies from the decision of the examining division to refuse European patent application 09 720 914.2 for lack of novelty pursuant to Article 54 EPC.

According to point 17 of the reasons, said decision was based on the set of claims filed as main request with the letter of 8 September 2015.

II. Document D1, cited in examination proceedings, was invoked by the appellant in written appeal proceedings.

D1: WO 2006/097474 A1

III. With the statement of grounds of appeal the appellant filed an experimental report, originally filed in examination proceedings with the letter of 12 November 2012, denoted in the following as D2.

IV. With the letter of 4 January 2021, in response to a communication of the board pursuant to Rule 100(2) EPC, the appellant filed a new set of claims as main request.

V. Requests

The appellant requests that the contested decision be set aside and that a patent be granted on the basis of the set of claims filed with the letter of 4 January 2021.

VI. Independent claim 1 of the main request reads as follows:

"*1. A salt of (E)-N-(2-amino-phenyl)-3-{1-[4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide, wherein the salt is toluenesulfonate.*"

Claim 3 is directed to the salt of claim 1 in a first medical use pursuant to Article 54(4) EPC. Claims 4 and 7 are directed to the salt of claim 1 in a second medical use pursuant to Article 54(5) EPC. Claim 5 is directed to a pharmaceutical composition comprising the salt of claim 1. Claim 6 is a Swiss-type second medical use claim comprising the use of the salt of claim 1 in the manufacture of pharmaceutical compositions.

VII. The arguments of the appellant, insofar as relevant to the present decision, may be summarised as follows:

Amendments - Article 123(2) EPC

The substitution within the compound name recited in claim 1 of the term "toluenesulfonyl", present in claim 1 of previously pending claim sets, with "benzenesulfonyl" in claim 1 of the main request was in accordance with the provisions of Article 123(2) EPC.

Novelty over document D1 - Article 54 EPC

In order to arrive at the salt of claim 1, several selections were required in D1. Compound 7 of claim 11 of document D1 had to be singled out from the 121 compounds mentioned therein, representing a one-dimensional shrinking of the list disclosed therein. There was no indication in D1 that this compound was to

be given a particular preference over the other compounds mentioned. Claim 11 of D1 also mentioned salts of the compounds recited. There was no indication in D1 that any particular salt may be specifically assigned to the compounds of claim 11. The reference to possible salts for the compounds of formula I (D1, page 32, final paragraph - page 33, second paragraph) did not refer specifically to the compounds of claim 11. The combination of the toluenesulfonate salt mentioned in the description as part of a list and compound 7 of claim 11 of D1 represented a specific selection from two lists which, according to the case law of the Boards of Appeal, was to be considered novel.

The subject-matter of claims 1-7 was consequently novel over the disclosure in D1.

Inventive step - Article 56 EPC

D1 represented the closest prior art to the subject-matter of claim 1 and differed therefrom in that it disclosed the hydrochloride salt of the compound recited.

The data presented in D2 demonstrated *inter alia* the improved solubility of the toluenesulfonate salt of claim 1 compared to the corresponding hydrochloride salt. The technical problem was the provision of an improved salt of (E)-N-(2-amino-phenyl-3-{1-[4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide. The solution to the problem, the provision of the salt of claim 1, involved an inventive step starting from D1 as closest prior art.

VIII. Since the board was in a position to grant the appellant's main request, there was no need to hold oral proceedings pursuant to Article 116(1) EPC.

Reasons for the Decision

Article 108 EPC - statement of grounds of appeal

1. The appellant filed a statement of grounds of appeal with the letter dated 8 November 2016 and a further "additional written statement setting out the grounds of appeal", filed on 14 November 2016. The latter was filed within the four month time limit of Article 108 EPC, third sentence, and comprised the submission of the former in its entirety. It may therefore be considered as the statement of grounds of appeal, rather than a further submission of the appellant. Consequently, reference to the "statement of grounds of appeal" in this decision refers exclusively to the submissions filed with the letter of 14 November 2016.

Main request

2. Basis for the contested decision

2.1 Although the contested decision mentioned a main request filed on 7 October 2015 (decision, paragraph 12), it also subsequently stated that the decision was based on *inter alia* the claim set filed on 8 September 2015 (decision, paragraph 17).

2.2 The question therefore arises as to which claim set actually formed the basis for the contested decision. This issue is of importance, since if it were to be found that the contested decision were based on a claim set different to that eventually put forward by the applicant (c.f. Article 113(2) EPC), a substantial procedural violation would have taken place.

2.3 Paragraph 18 of the contested decision addresses novelty with regard to D1, specifically the disclosure therein of an acrylamide compound comprising a "benzenesulfonyl" moiety, and the corresponding salts thereof. This disclosure, in combination with the disclosure in the description of D1 of a specific salt, was considered novelty destroying for the subject-matter of claim 1 of the then main request. Claim 1 of the set filed as main request on 7 October 2015 also discloses an acrylamide having a "benzenesulfonyl" moiety, while claim 1 of the set filed on 08 September 2015 referred to a compound having a “toluenesulfonyl” moiety. It must therefore be concluded that the contested decision is based on the set of claims filed as main request on 7 October 2015, despite the erroneous reference to a different set of claims in paragraph 17 thereof. Thus a substantial procedural violation did not occur.

2.4 The set of claims of the main request in the present appeal proceedings is identical to that filed as main request during examination proceedings with the letter dated 7 October 2015, with the exception that in claims 3-6, the term "salts" has been amended to "salt".

3. Amendments - Request for correction under Rule 139 EPC & Article 123(2) EPC

3.1 Claim 1

3.1.1 The appellant submitted that an obvious error had been corrected by substitution of the moiety "toluenesulfonyl" with the corrected "benzenesulfonyl" within the name of the compound of claim 1 of the main request.

This amendment indeed represents a correction compared to some claim sets previously on file, e.g the respective claim 1 of the claim sets filed with the letters of 20 January and 7 September 2015. For compliance with Article 123(2) EPC however, and thus also Rule 139 EPC, what is decisive is whether the amendment or correction is directly and unambiguously derivable from the content of the **application as filed**.

3.1.2 In the present case, the subject-matter of claim 1 of the main request is identical to the alternative disclosed in claim 1 of the application as filed wherein the salt is toluenesulfonate. Hence, the subject-matter of claim 1 of the main request does not constitute a correction compared to the application as filed, and furthermore complies with the requirements of Article 123(2) EPC.

3.2 Claims 2-7

Claim 2 of the main request finds basis in claim 5 of the application as filed in combination with page 12, lines 3-4 describing the X-ray diffraction method recited in the claim. Claims 3, 4, 5 and 6 correspond to claims 7, 8, 10 and 11 of the application as filed,

respectively. Claim 7 corresponds to claim 13 of the application as filed, re-worded as a second medical use claim pursuant to Article 54(5) EPC.

Furthermore, the amendment in claims 3-6 of the term "salts" to "salt" merely represents a clarifying amendment resulting from the limitation of claim 1 to a single salt.

It follows that the claims of the main request meet the requirements of Article 123(2) EPC.

4. Novelty - Article 54 EPC

4.1 Claim 1 of the main request refers to a salt of (E)-N-(2-amino-phenyl)-3-{1-[4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide, wherein the salt is toluenesulfonate. The salt thus comprises the above acrylamide, protonated, as the cation and toluenesulfonate as the anion (resulting from the deprotonation of toluenesulfonic acid).

4.2 According to the contested decision, claim 1 of the main request lacked novelty over D1.

4.3 D1 is a patent document which discloses in claim 1 compounds of formula I, defined by a broad Markush formula, and the salts of those compounds (D1, pages 163-166). Claim 11, dependent on claim 1, is directed to a list of 121 specific compounds, or salts thereof (D1, pages 179-185). Compound 7 in this list corresponds to the cation of the salt of claim 1 at issue.

4.4 Suitable anions (resulting from acids) for the compounds of formula I of D1 are provided in the description in the form of an extensive list (page 32, final paragraph - page 33, first paragraph):

"... Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid such as (-)-L-malic acid or (+)-D-malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid such as (+)-L-tartaric acid or (-)-D-tartaric acid or mesa-tartaric acid, embonic acid, stearic acid, ***toluenesulphonic acid****, methanesulphonic acid or 3-hydroxy-2-naphthoic acid ..."* (emphasis added by the board);

and

"... further acids, which may be used in the preparation of possible salts of compounds of formula I, can be mentioned any selected from adipic acid, L-ascorbic acid, L-aspartic acid, benzenesulfonic acid, 4-acetamido-benzoic acid, (+)-camphoric acid, (+)-camphor-10-sulfonic acid, caprylic acid (octanoic acid), dodecylsulfonic acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, galactaric acid, gentisic acid, D-glucoheptonic acid, D-glucuronic acid, glutamic acid, 2-oxo-glutaric acid, hippuric acid, lactic acid such as

D-lactic acid or L-lactic acid, malonic acid, mandelic acid such as (+)-mandelic acid or (-)-mandelic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, nicotinic acid, palmitic acid, pyroglutamic acid such as L-pyroglutamic acid, hydroiodic acid, cyclamic acid, thiocyanic acid, 2,2-dichloroacetic acid, glycerophosphoric acid, 1-hydroxy-2-naphthoic acid, salicyclic acid, 4-aminosalicyclic acid, glycolic acid, oleic acid, glutaric acid, cinnamic acid, capronic acid, isobutyric acid, propionic acid, capric acid, undecylenic acid and orotic acid."

The toluenesulphonic acid (in bold, above), and more specifically, the toluenesulfonate anion thereof, corresponds to the anion of the salt defined in claim 1 of the main request.

4.5 Hence in order to arrive at the subject-matter of claim 1 of the main request, one must select (i) compound 7 from the 121 compounds listed in claim 11, (ii) a salt thereof rather than the free acrylamide compound, and (iii) toluenesulphonic acid from the long list of possible acids disclosed on pages 32 and 33 of D1.

4.6 According to the contested decision, the choice of compound 7 from claim 11 of D1 as the cation, in combination with the choice of toluenesulfonate as a suitable anion, taken from the list on page 32, did not amount to a selection from two independent lists, which would have rendered claim 1 at issue novel. Rather, the examining division was of the opinion (decision, paragraph 18) that

"... *the presentation of the specific compounds* [in claim 11 of D1] *does not mean that one has to select from this list, in the meaning of the selection of a feature, but that* ***each*** *specific compound is a most highly preferred embodiment of the disclosure of D1*".

Thus, according to the examining division, the subject-matter of claim 1 at issue resulted from a choice in D1 of a preferred compound (compound 7 of claim 11) as the cation, in combination with toluenesulfonic acid as the anion, chosen from a single list. This selection was seen to lack novelty.

4.7 The board disagrees. Dependent claim 11 of D1 concerns a list of specific compounds. While those compounds may indeed be seen as "preferred" embodiments falling within the scope of compounds of formula I defined by way of a broad Markush formula in independent claim 1 of D1, this does not detract from the fact that the list comprises 121 members. None of the members of said list are singled out in D1 (neither in the claims nor elsewhere in the disclosure) as being particularly preferred over the other compounds listed, either individually or as members of a more limited list. Since there is no distinction between the level of preference assigned in D1 to each of the 121 compounds of claim 1, the board sees no reason not to consider claim 11 as comprising a list of (equally) preferred embodiments from which a selection is still required in order to arrive at the selection of the free acrylamide compound corresponding to the salt cation of claim 1 at issue.

4.8 In addition to the first and second selections (i) and (ii) outlined above, a further selection of "toluenesulfonic acid" as the specific salt anion from

the long list of possible salts disclosed on page 32 and 33 of the description of D1 is required to arrive at the subject-matter of claim 1 at issue. Among the salts disclosed, only the hydrochloric acid salt is singled out from the acids listed (D1, page 33, fifth paragraph; example 7), while for all other possible salt anions including that resulting from toluenesulfonic acid, no preference for one over another is expressed in D1.

4.9 Since in order to arrive at the subject-matter of claim 1 a selection is required in D1 from two lists of significant length, in combination with a further selection in D1 of a salt over the free acrylamide compound (selection (ii), above), the subject-matter of claim 1 is to be regarded as novel. This is in line with the "two-list principle" established in landmark decision T 12/81, and generally applied consistently in the jurisprudence of the boards of appeal.

4.10 Moreover, the board agrees with the appellant that the standard of disclosure must be the same for assessing the requirements of Articles 123(2) and 54 EPC. This is in line with the uniform concept of disclosure (the "gold standard") for the purposes of assessing aspects of novelty (Article 54 EPC), validity of the claimed priority (Article 87 EPC) and added subject-matter (Article 123(2) EPC). These standards were established in *inter alia* G 2/88 (reasons, 8.4), G 3/89 (reasons, 3), G 1/03 (reasons 2.2.2) and G 2/10 and confirmed in G 1/16 (e.g. reasons, 17). Applying this standard, the board concurs with the appellant that a hypothetical amended claim in D1 directed to the subject-matter of claim 1 at issue would contravene the requirements of Article 123(2) EPC.

It follows from the foregoing that the subject-matter of claim 1, and by the same token of all remaining claims of the main request, is novel with respect to D1.

5. Inventive step - Article 56 EPC

5.1 In view of the conclusion that the claimed subject-matter lacked novelty, inventive step was not addressed in the contested decision. Nevertheless, during examination proceedings, the examining division considered D1 as the closest prior art for the purpose of assessing inventive step (e.g. communication pursuant to Article 94(3) EPC dated 24 February 2016, section 5).

5.2 Closest prior art

5.2.1 Similarly to the present application, D1 discloses compounds as effective inhibitors of histone deacetylases (HDACs; page 5, first paragraph). D1 is identified in the present application (page 6, final paragraph) as disclosing the "compound with hydrochloric acid", i.e. the hydrochloride salt of the free acrylamide of claim 1 at issue (D1, page 109, example 7). The problem mentioned in the present application is that the compounds of D1 suffer from a relatively low solubility and/or high hygroscopicity (application, page 7, lines 1-5). D1 is thus a suitable closest prior art disclosure in the assessment of inventive step of the claimed subject-matter.

5.2.2 The compound corresponding to the acrylamide cation of claim 1 is disclosed twice in D1. Firstly, as the hydrochloride salt mentioned above, and secondly in

claim 11 (compound 7) as the free acrylamide compound. The hydrochloride salt of example 7 is however closer to the subject-matter of claim 1 since it represents a specifically prepared compound of D1, and similarly to the claimed compound, is a salt. The assessment of inventive step for the subject-matter of claim 1 is therefore to be carried out vis à vis this compound.

5.3 Problem solved

5.3.1 The subject-matter of claim 1 at issue is distinguished from example 7 of D1 in the nature of the salt anion, which according to claim 1 at issue is toluenesulfonate.

5.3.2 As set out above (point 5.2.1), according to the application as filed, the problem to be solved lies in the provision of a compound with improved solubility and/or hygroscopicity compared to that in D1.

5.3.3 In experimental report D2, the dissolution profile of a hydrochloride salt corresponding to that of example 7 of D1 was compared with that of the salt of claim 1 at issue. The results demonstrate that the latter (figure, curve for "toluol sulfonate") dissolves faster in phosphate buffer than the former (figure, curves for "dihydrochloride"). Thus the problem mentioned in the patent application, at least with respect to improved solubility, has been solved by the subject-matter of claim 1.

5.3.4 The objective technical problem is consequently the provision of a form of (E)-N-(2-amino-phenyl)-3-{1-[4-(1-methyl-1H-pyrazol-4-yl)-benzenesulfonyl]-1H-pyrrol-3-yl}-acrylamide with improved solubility compared to the prior art hydrochloride form.

5.4 Obviousness

5.4.1 Although as addressed above under novelty, the toluenesulfonate salt is mentioned in D1 in a long list of possible salts, there is no indication therein nor elsewhere which would lead the skilled person, wishing to solve the above-mentioned problem, to this choice from among the many possibilities listed.

5.4.2 It follows therefore that the subject-matter of claim 1 involves an inventive step. Being either dependent on claim 1 or referring back to it, the same conclusion applies to all subsequent claims 2-7.

The set of claims of the main request consequently involves an inventive step.

6. Sufficiency of disclosure

6.1 The preparation of polymorphic forms A-H according to claim 2 at issue is described on pages 23-24 of the application. Hence the board does not see any reason to doubt that the application as filed enables the skilled person to prepare the claimed salts (claims 1 to 3) and the claimed composition (claim 5). The specifically claimed medical uses (claims 3, 4, 6 and 7) of the *cation* of the claimed compound (the active species) are already known from D1 (e.g. paragraph bridging pages 143 and 144), and biological tests have confirmed this activity (e.g. pages 160-162, table 2-4). Hence, the requirements of Article 83 EPC are fulfilled.

7. Article 84 EPC - clarity

With the claims of the main request, the only clarity objection raised in the board's communication was overcome by the amendment in claims 3-6 of the request previously on file. More specifically, the plural "salts" was amended to the singular "salt", in reference to the sole salt recited in claim 1. The claims of the main request thus meet the requirements of Article 84 EPC.

8. Conclusion

The set of claims of the main request filed with the letter dated 4 January 2021 is consequently allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description to be adapted thereto:

   Claims 1-7 filed with the letter dated 4 January 2021.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated