BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | **BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE** | **CHAMBRES DE RECOURS DE L'OFFICE EUROPÉEN DES BREVETS**

Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision
of 18 September 2025

Case Number:	T 1426/23 - 3.3.02
Application Number:	16879990.6
Publication Number:	3393655
IPC:	B01J23/72, B01J27/055, B01J27/122, B01J27/25, C07C45/54, C07C49/223, C07C209/28, C07C211/29, C07C51/43
Language of the proceedings:	EN

Title of invention:
FENFLURAMINE COMPOSITIONS AND METHODS OF PREPARING THE SAME

Patent Proprietor:
Zogenix International Limited

Opponents:
OLON S.p.A.
Kraus & Lederer PartGmbB

Relevant legal provisions:
EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:
Inventive step
Amendment after notification of the board's communication under Article 15(1) RPBA

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 1426/23 - 3.3.02

DECISION
of Technical Board of Appeal 3.3.02
of 18 September 2025

Appellant: (Opponent 2)	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Patent Proprietor)	Zogenix International Limited Windlesham Campus, Sunninghill Road Windlesham, Surrey GU20 6PP (GB)
Representative:	Leonard, Thomas Charles Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Party as of right: (Opponent 1)	OLON S.p.A. Strada Rivoltana Km. 6/7 20090 Rodano (MI) (IT)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 July 2023 rejecting the opposition filed against European patent No. 3393655 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	L. Bühler

Summary of Facts and Submissions

I. Opponent 2 (appellant) lodged an appeal against the opposition division's decision (decision under appeal) to reject the opposition against European patent No. 3 393 655 (patent).

II. Reference is made in the present decision to the following documents filed with the opposition division:

D2	Journal of Organic Chemistry, Vol. 71, No. 17, 2006, pages 6640 to 6643
D4	Chemical Journal of Chinese Universities, Vol. 9, No. 2, 1988, pages 134 to 139
D4a	English translation of D4
D11	Journal of Shenyang College of Pharmacy, Vol. 11, No. 2, 1994, pages 116 to 118
D11a	English translation of D11
D12	Journal of Medicinal Chemistry, Vol. 29, No. 6, 1986, pages 924 to 939

For the sake of brevity, only the respective translations of documents D4 and D11 are referred to below.

III. In preparation for the oral proceedings, which had been arranged at the parties' request, the board issued a communication under Article 15(1) RPBA.

IV. With its letter dated 16 June 2025, the patent proprietor (respondent) filed, *inter alia*, the set of claims of auxiliary request 13.

V. Oral proceedings before the board were held by videoconference on 18 September 2025 in the presence of the appellant and the respondent.

The respondent promoted its auxiliary request 13 filed with letter dated 16 June 2025 to its auxiliary request 4b. The board decided to admit auxiliary request 4b into the proceedings. During the discussion of inventive step, the board decided to admit neither the appellant's reformulation of the objective technical problem as a mere alternative, nor any related submission made by the appellant during the oral proceedings leading to the reformulation. Apart from the claims as granted and auxiliary request 4b, the respondent withdrew all other pending claim requests.

At the end of the oral proceedings, the chair announced the order of the present decision.

VI. Opponent 1 did not file any submissions or requests during the appeal proceedings.

The appellant's and the respondent's final requests at the end of the oral proceedings were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.
- The respondent requested that the appeal be dismissed, implying that the decision under appeal be confirmed and the patent be maintained as granted (main request). In the alternative, it requested that the patent be maintained in amended form based on the set of claims of auxiliary

request 4b, filed as auxiliary request 13 with its letter dated 16 June 2025.

VII. Summaries of the parties' submissions relevant to the present decision and key aspects of the decision under appeal are set out in the reasons for the decision below.

Reasons for the Decision

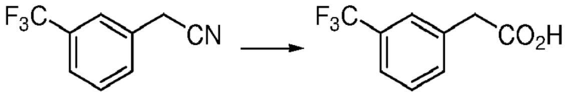
Main request (patent as granted) - Inventive step (Article 56 EPC)

1. Claim 1 of the main request reads as follows:

> "*A method of preparing a fenfluramine active pharmaceutical ingredient, the method comprising:*
>
> *(a) hydrolyzing a 2-(3-(trifluoromethyl)phenyl)-acetonitrile composition to produce a 2-(3-(trifluoromethyl)phenyl)acetic acid composition;*
>
> *(b) reacting the 2-(3-(trifluoromethyl)phenyl)-acetic acid composition with acetic anhydride and a catalyst to produce a 1-(3-(trifluoromethyl)-phenyl)propan-2-one composition; and*
>
> *(c) reductively aminating the 1-(3-(trifluoromethyl)phenyl)propan-2-one composition with ethylamine using a borohydride reducing agent to produce a fenfluramine composition.*"

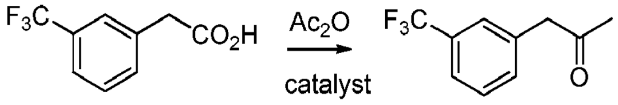
2. The method of preparing fenfluramine according to claim 1 can also be represented by structural formulae as follows:

step (a) of claim 1:



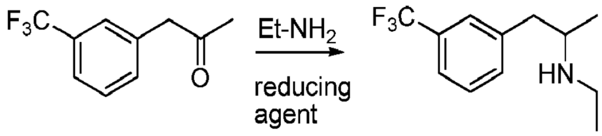
(5) (4)

step (b) of claim 1:



(4) (2)

step (c) of claim 1:



(2) (1)

Hereafter, the respective compounds may be referred to by the number shown above below each compound (taken from paragraph [0036] of the patent). For example, fenfluramine is compound (1). Compounds (4) and (2) are referred to by their functional groups, i.e. acid (4) and ketone (2), which are relevant in the present case.

As is evident from the formulae above, the trifluoromethyl group and the other substituents on the benzene ring, the modification of which ultimately gives rise to fenfluramine, are meta-oriented relative to each other. The compounds in which these substituents are in ortho- or para-orientation are referred to as regioisomers in this decision.

In line with the parties, the generalised reaction of step (b), i.e. the conversion of a substituted acetic acid into a substituted acetone using acetic anhydride and a catalyst, is referred to as the Dakin-West reaction.

3. Closest prior art, distinguishing feature and technical effect

The following points were common ground between the parties.

- The synthesis of fenfluramine disclosed in D11a (reaction scheme on page 2; steps 1.3 to 1.5 on page 3 f.) can be considered to be the closest prior art in the present case.
- The subject-matter of claim 1 of the main request differs from the synthesis of fenfluramine disclosed in D11a in step (b). More specifically, the reagents used for the conversion of acid (4) to ketone (2) are different: acetic anhydride and a catalyst in step (b) of claim 1 of the main request, methyllithium (MeLi) in step 1.4 of D11a.
- The distinguishing feature above is not associated with a technical effect.

The board notes that, although the respondent had agreed that no technical effect was achieved, it nevertheless argued in its reply to the statement of grounds of appeal (see point 5.3.6) that the Dakin-West reaction enabled the preparation of ketone (2) in higher yield and purity than other known methods. However, as the appellant rightly pointed out, this argument is irrelevant in the present case, since it is not based on a comparison with the synthesis disclosed in the closest prior art, where ketone (2) is obtained from acid (4) using MeLi. Rather, the respondent's argument concerns an alternative synthetic route, in which ketone (2) is produced from a diazonium intermediate.

4. Objective technical problem

On appeal, the respondent concurred with the opposition division that the objective technical problem was to provide an alternative method of preparing fenfluramine. This is accepted in the respondent's favour below.

5. Obviousness

5.1 Faced with the problem of providing an alternative method of preparing fenfluramine, the skilled person would, for example, have considered modifying the reaction conditions for the conversion of acid (4) into ketone (2). As set out above, this conversion is carried out in D11a using MeLi.

5.2 In a search aimed at identifying other possible reaction conditions for the conversion of acid (4) into ketone (2), the skilled person would have come across D2. This was undisputed between the parties.

In view of its aim, such a search would not have been limited to prior art relating to the synthesis of fenfluramine. Therefore, it is not surprising and, contrary to the respondent's argument, entirely irrelevant to the assessment of inventive step that D2 does not relate to the synthesis of fenfluramine.

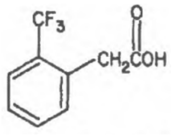
5.3 D2 (table 1) investigates the Dakin-West reaction with regard to both catalysts and substrates. 1-Methylimidazole (MIM) is stated to be a favourable catalyst as it enables the successful conversion of a wide range of substrates, including some generally regarded as challenging. Some of these substrates are structurally very similar to acid (4) of claim 1, namely phenylacetic acid, para-nitrophenylacetic acid and para-methoxyphenylacetic acid (table 1, entries 2, 9 and 10).

It is true, as argued by the respondent and as held by the opposition division, that D2 does not investigate meta-substituted phenylacetic acids as substrates, let alone acid (4). However, given the broad applicability of MIM as a catalyst as shown in D2, the board agrees with the appellant that the skilled person would still have had a reasonable expectation that, by using this catalyst together with acetic anhydride, acid (4) could be successfully converted into ketone (2) in a Dakin-West reaction. They would thereby have arrived at the subject-matter of claim 1 of the main request in an obvious manner.

The board observes that the respondent's argument, insofar as it relies on the absence in D2 of a disclosure of the claimed Dakin-West reaction converting acid (4) to ketone (2), ultimately implies that a claimed multistep synthesis might be considered inventive merely because one individual step of that synthesis using both the claimed starting material(s) and reagent(s) had not previously been disclosed in the prior art. In the opinion of the board, this is far too low a threshold and is unconvincing.

5.4 The respondent submitted the following additional arguments.

5.4.1 According to the respondent, D12 (scheme IV, reaction (b); table I, entry 12c) disclosed that the Dakin-West reaction of the ortho-regioisomer of acid (4), i.e.



,

produced the corresponding ketone in a yield of only 17%. By contrast, D12 also reported that phenylacetic acid derivatives other than the ortho-regioisomer mentioned above afforded the corresponding ketones in yields exceeding 17% when reacted with MeLi. Therefore, the skilled person considering D12 would not have chosen the inferior Dakin-West reaction for the transformation of acid (4) to ketone (2). This argument also seems to have prompted the opposition division to recognise an inventive step.

However, this argument is unconvincing for at least the following reasons.

- D12 may indeed disclose only a low yield for the reaction of the ortho-regioisomer depicted above and thus lead the skilled person to expect that the conversion of the meta-isomer, i.e. acid (4), will also result in only a low yield. However, as argued by the appellant, a low yield of ketone (2) does not alter the skilled person's expectation of successfully solving the objective technical problem, as this is formulated in the most unambitious way, such that it does not require a minimum yield in step (b).
- Even if it were assumed - contrary to the above - that the respondent's argument with respect to D12

were convincing, the fact that the claimed subject-matter is inventive over the combination of D11a with D12 does not invalidate the conclusion of a lack of an inventive step over the combination of D11a with D2. It should be noted that D12 is simply a single journal article and as such does not constitute any prejudice in the art against applying the above-discussed teaching of D2 to D11a.

Irrespective of the above, and merely as an additional comment, the board notes that the Dakin-West reaction of the ortho-regioisomer of acid (4) was carried out in D12 using pyridine as the catalyst. However, D2 (table 1, entries 1 and 2) itself describes pyridine as an inferior catalyst compared to MIM. For this reason too, the results reported in D12 cannot affect the expectation of success that the skilled person would have had based on D2.

For the same reasons set out above (namely, that the objective technical problem does not require any particular performance or yield), the respondent’s further argument that performance was strongly influenced by the different substituents on the phenyl ring is likewise unconvincing.

5.4.2 The respondent further argued that, in order to arrive at the subject-matter of claim 1, the skilled person would have had to specifically choose to modify step 1.4, rather than any of the other steps of the synthesis disclosed in D11a. Likewise, D2 and D12 taught that ketones could be obtained by various methods and therefore application of the Dakin-West reaction would have required an additional specific choice among these alternatives. The necessity of such specific selections showed that the subject-matter of claim 1 of the main request was based on an inventive step.

However, in the absence of any convincing arguments as to why modifying the other steps of the synthesis disclosed in D11a (i.e. steps 1.3 and 1.5) or why using the other methods for the synthesis of ketones disclosed in D2 and D12 (i.e. methods other than the Dakin-West reaction) would not have been equally suitable for solving the objective technical problem in the present case, each of the synthesis steps of D11a and each of the methods of D2 and D12 would have appeared to be an obvious option to the skilled person. The board agrees with the appellant that the mere selection of one step and one method from among a number of obvious alternatives cannot confer inventiveness on the subject-matter of claim 1 of the main request.

5.5 Accordingly, the subject-matter of claim 1 does not involve an inventive step and the main request is not allowable.

Auxiliary request 4b - Admittance (Article 13(2) RPBA)

6. The respondent filed auxiliary request 4b with its letter dated 16 June 2025, i.e. after its reply to the statement of grounds of appeal. It was common ground between the parties that the filing of auxiliary request 4b amounted to an amendment to the respondent's appeal case.

At the oral proceedings, the board decided to admit auxiliary request 4b into the proceedings, contrary to the appellant's request in this respect. The reasons are as follows.

6.1 In its statement of grounds of appeal, the appellant raised an objection under Article 100(c) EPC to the subject-matter of dependent claims 6 and 7 of the main request.

6.2 Claims 6 and 7 of the main request refer back to independent claim 1 and, *inter alia*, additionally define an upper threshold of less than 0.2% by weight for trifluoromethyl-phenyl regioisomers of fenfluramine or their salts in the crude reaction product (for the wording of claim 1, see above).

6.3 More specifically, the appellant argued that the sentence spanning lines 12 to 16 of paragraph [0047] of the application as filed did not provide a basis for this definition. In this sentence, the upper threshold value of 0.2% by weight referred only to trifluoromethyl-phenyl regioisomers of fenfluramine but not also to their salts, in contrast to claims 6 and 7 of the main request.

6.4 In its communication under Article 15(1) RPBA, the board did not address the merits of the appellant's objection. Instead, it stated that the subject-matter of claims 6 and 7 of the main request seemed to extend beyond the content of the application as filed for another reason. In the aforementioned sentence (paragraph [0047], lines 12 to 16), the upper weight threshold referred to a composition comprising a pharmaceutically acceptable salt of fenfluramine. The subject matter of claims 6 and 7 of the main request, on the other hand, was not limited accordingly and left open the possibility that no salt of fenfluramine was present.

6.5 Contrary to the appellant's submission, the fact that the objections raised by the board and the appellant were based on the same sentence in paragraph [0047] of the application as filed does not alter the fact that the board's objection differed from that of the appellant and was therefore new. Such a new objection constitutes exceptional circumstances within the meaning of Article 13(2) RPBA, to which the respondent had to be able to respond. It did so swiftly with auxiliary request 4b, from which both claims at issue were deleted.

Auxiliary request 4b - Amendments (Article 123(2) EPC) and sufficiency of disclosure (Article 83 EPC)

7. As set out above, the appellant objected to the subject-matter of claims 6 and 7 of the main request under Article 100(c) EPC. It also raised an objection under Article 100(b) EPC to claim 3 of the main request.

Claims 3, 6 and 7 of the main request have been deleted in the set of claims of auxiliary request 4b. Therefore, the appellant's objections to these claims are no longer relevant to auxiliary request 4b.

Auxiliary request 4b - Inventive step (Article 56 EPC)

8. Claim 1 of auxiliary request 4b reads as follows (the additional features compared to claim 1 of the main request are shown in bold):

> "*A method of preparing a fenfluramine active pharmaceutical ingredient, the method comprising:*
>
> *(a) hydrolyzing a 2-(3-(trifluoromethyl)phenyl)-acetonitrile composition to produce a 2-(3-(trifluoromethyl)phenyl)acetic acid composition;*
> ***(ai) purifying the 2-(3-(trifluoromethyl)phenyl)-acetic acid composition to produce a composition substantially devoid of one or more trifluoromethyl-phenyl regioisomers and substantially devoid of trifluoromethylbenzaldehyde and benzaldehyde, wherein the purifying comprises crystallization of 2-(3-(trifluoromethyl)phenyl)acetic acid from the composition;***
>
> *(b) reacting the 2-(3-(trifluoromethyl)phenyl)-acetic acid composition with acetic anhydride and a catalyst to produce a 1-(3-(trifluoromethyl)-phenyl)propan-2-one composition,* ***wherein step (b) comprises purification of the 1-(3-(trifluoromethyl)phenyl)propan-2-one composition via a ketone bisulfite adduct;*** *and*
>
> *(c) reductively aminating the 1-(3-(trifluoromethyl)phenyl)propan-2-one composition with ethylamine using a borohydride reducing agent to produce a fenfluramine composition.*"

Thus, the subject-matter of claim 1 of auxiliary request 4b differs from that of claim 1 of the main request in two additional purification steps. In line with their order of appearance in the claim, these are hereinafter respectively referred to as the first and second purification steps.

9. Closest prior art and distinguishing feature

Both parties considered that the synthesis of fenfluramine disclosed in D11a (reaction scheme on page 2; steps 1.3 to 1.5 on page 3 f.) also represents the closest prior art for the subject-matter of claim 1 of auxiliary request 4b.

They also agreed that the subject-matter of claim 1 of auxiliary request 4b differs from the synthesis disclosed in D11a not only in that step (b) is carried out with different reagents (same distinguishing feature as discussed above for the main request), but also at least in that the second purification step - i.e. purification via a ketone bisulfite adduct - is not disclosed in D11a.

10. Technical effect and objective technical problem

10.1 The respondent pointed to the experimental data discussed on pages 23 to 24 of its reply to the statement of grounds of appeal. These data show an increase in purity and a removal of regioisomers upon purification of ketone (2) via its bisulfite adduct. This was not questioned by the appellant.

10.2 On this basis, the objective technical problem is that advanced by the respondent, namely to provide an improved method of preparing fenfluramine in which the method results in increased purity and removal of regioisomers.

10.3 The appellant did not agree with this objective technical problem. More specifically, it argued that it was *prima facie* apparent that the data in the respondent's reply were not a proper comparison with the closest prior art D11a. Therefore, a technical effect could not be acknowledged and the objective technical problem was, if anything, still the same as that formulated by the respondent for the subject-matter of claim 1 of the main request, i.e. to provide an alternative method of preparing fenfluramine.

However, the appellant's criticism of the respondent's data in its reply as not being a proper comparison with D11a was put forward only at the oral proceedings before the board. As argued by the respondent, and not in fact contested by the appellant, this submission amounted to an amendment to the appellant's appeal case and this amendment was made only at the oral proceedings before the board. Article 13(2) RPBA stipulates that such an amendment shall not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned. However, the appellant did not put forward any argument which could be understood as exceptional circumstances in the present case. In particular, the *prima facie* relevance of a submission is, contrary to the appellant's argument, irrelevant to the question of whether there are exceptional circumstances. Therefore, at the respondent's request, the board decided at the oral proceedings to admit neither the reformulation of the objective technical problem by the appellant as a mere alternative, nor any related submission made by the appellant during the oral proceedings leading to this reformulation. The conclusion regarding the objective technical problem under the previous point thus remains valid.

11. Obviousness

In the appellant's view, the solution to the objective technical problem would have been obvious to the skilled person based on D4a.

D4a (page 19/43, third paragraph ff.) describes the synthesis of ketone (2) through a pathway different from that disclosed in the patent. Specifically, ketone (2) is not obtained from an acid using a Dakin-West reaction but by oxidizing the corresponding secondary alcohol. Since this alcohol is in fact a mixture of alcohols, D4a recommends purifying ketone (2) via its bisulfite adduct. However, this represents the sole instance in D4a of such a purification, and it is limited to a specific substance mixture which does not contain regioisomers as defined in the present decision. D4a also does not emphasise the general applicability of purification via the bisulfite adduct. The board therefore concurs with the respondent that it would at the very least not have been obvious to the skilled person that the purification of ketone (2) via its bisulfite adduct would also permit separation of its regioisomers.

Therefore, the subject-matter of claim 1 and its dependent claims 2 to 11 is based on an inventive step and auxiliary request 4b is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent with the following claims and a description and drawings possibly to be adapted thereto: claims 1 to 11 of auxiliary request 4b, filed as auxiliary request 13 with the letter dated 16 June 2025.

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