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Datasheet for the decision of 19 July 2022

Case Number:	T 0027/20 - 3.3.02
Application Number:	10792677.6
Publication Number:	2445502
IPC:	C07D263/58, C07D401/12, C07D417/12, C07D471/04, C07F9/6558, C07D215/227, A61K31/497
Language of the proceedings:	EN

Title of invention:

HETEROCYCLIC COMPOUNDS FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHOLOGICAL DISORDERS

Patent Proprietor:

Alkermes Pharma Ireland Limited

Opponent:

Generics (UK) Ltd

Relevant legal provisions:

EPC Art. 56
EPC R. 103(1)(a), 111(2)

Keyword:

Inventive step
Substantial procedural violation - appealed decision reasoned (no)

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Case Number: T 0027/20 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 July 2022

Appellant: (Patent Proprietor)	Alkermes Pharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 (IE)
Representative:	Harris, Jennifer Lucy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Appellant: (Opponent)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 October 2019 concerning maintenance of the European Patent No. 2445502 in amended form**

Composition of the Board:

Chairman	P. O'Sullivan
Members:	A. Lenzen
	M. Blasi

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the patent proprietor (appellant) against the interlocutory decision of the opposition division (decision under appeal) according to which European patent no. 2 445 502 (patent) in amended form meets the requirements of the EPC.

A notice of appeal was filed by the opponent. The appeal was withdrawn with the letter of 5 February 2020, the opponent becoming respondent in the present proceedings.

II. The following documents are referred to in this decision:

D37 EP 0 367 141 A2

D43 Bristol Myers Squibb information leaflet about Abilify® (39 pages)

D53 Pitman, I. H., Pro-Drugs of Amides, Imides, and Amines, Medicinal Research Reviews, 1981, 1(2), pages 189 to 214

D56 Prescribing information about Aristada® (34 pages)

D58 Rautio, J. et al., Prodrugs: design and clinical applications, Nature Reviews, 2008, 7, pages 255 to 270

III. The decision under appeal is based, *inter alia*, on sets of claims of a main request and a first auxiliary request, both filed by letter of 16 August 2018. The opposition division decided that neither request was allowable.

IV. In its statement of grounds of appeal, the appellant continued to pursue the claim requests on which the decision under appeal is based, and resubmitted copies thereof.

V. By letter dated 16 July 2021, the respondent indicated that it would not attend the scheduled oral proceedings.

VI. In preparation for the oral proceedings, scheduled at the appellant's request, the board issued a communication pursuant to Article 15(1) RPBA 2020.

VII. By letter dated 9 May 2022, the appellant withdrew the main request, and declared the first auxiliary request to be its new main request. It also filed an adapted description for completeness and streamlining purposes.

VIII. The board then cancelled the oral proceedings.

IX. The parties' requests relevant to the present decision are as follows.

The appellant requests that the decision under appeal be set aside and that the patent be maintained in amended form based on the set of claims of the main request filed as the first auxiliary request with the statement of grounds of appeal.

The respondent requests that the appeal be dismissed.

X. The appellant's case relevant for the present decision can be summarised as follows.

The disclosure of aripiprazole in D37 or D43 represented the closest prior art. The subject-matter

of claim 1 of the main request differed from aripiprazole in that the δ-lactam nitrogen atom was bound to a substituent R_5 instead of a hydrogen atom. For compounds according to claim 1 without a double bond in conjugation with the δ-lactam carboxyl group, the experimental data in the patent demonstrated that *in vivo*, the substituent R_5 was replaced by a hydrogen atom, thus yielding the known antipsychotic drug aripiprazole disclosed in D37 and D43. Similarly, compounds according to claim 1 having a double bond in conjugation with the δ-lactam carboxyl group released dehydro aripiprazole *in vivo*. As was evident from D56, dehydro aripiprazole had a similar antipsychotic activity to aripiprazole. The compounds of claim 1 were thus prodrugs of the antipsychotic drugs aripiprazole/ dehydro aripiprazole, and the objective technical problem was therefore to provide prodrugs of aripiprazole/dehydro aripiprazole. The skilled person would not have had a reasonable expectation of success that the presence of a substituent R_5 on the δ-lactam nitrogen atom of aripiprazole/dehydro aripiprazole would have resulted in prodrugs thereof. Consequently, the subject-matter of claim 1 of the main request involved an inventive step.

The absence of any reasoning in the decision under appeal as to why the main request was not allowable amounted to a substantial procedural violation.

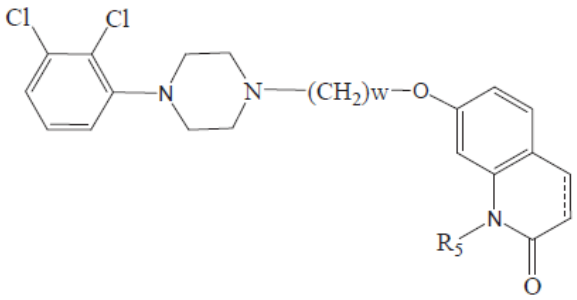
XI. The respondent did not make any submissions on the merits of the appeal.

Reasons for the Decision

Main request

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

"*A compound represented by Formula V:*



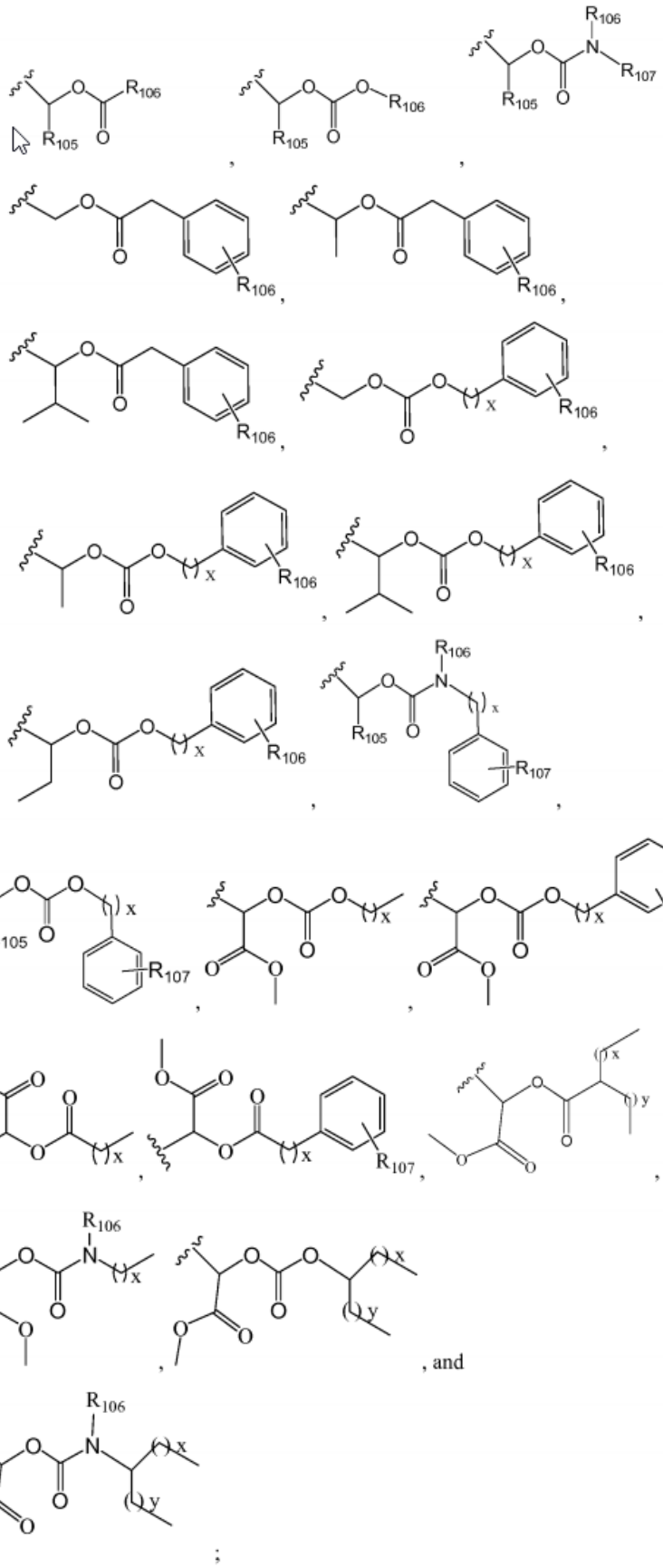
Formula V

or its geometric isomers, enantiomers, diastereomers, racemates, pharmaceutically acceptable salts and solvates thereof,

wherein ---------- *represents a single or a double bond;*

w is 4;

R_5 is selected from $-CH(R_{10})-OC(O)OR_{20}$, $-CH(R_{10})-OC(O)R_{20}$, $-CH(R_{10})-OC(O)NR_{20}R_{21}$,



, and

;

[...]
each R_{20} and R_{21} is independently selected from hydrogen, aliphatic, substituted aliphatic, aryl or substituted aryl;
each x and y is independently an integer between 0 and 30,
[...]
R_{105}, R_{106} and R_{107} are independently selected from hydrogen, halogen, optionally substituted C_1-C_{24} alkyl, optionally substituted C_2-C_{24} alkenyl, optionally substituted C_2-C_{24} alkynyl, optionally substituted C_3-C_{24} cycloalkyl, optionally substituted C_1-C_{24} alkoxy, optionally substituted C_1-C_{24} alkylamino and optionally substituted C_1-C_{24} aryl;
R_{10} is hydrogen, halogen, aliphatic, substituted aliphatic, aryl or substituted aryl; and
wherein "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with the radical of a specified substituent selected from halo, alkyl, alkenyl, alkynyl, aryl, heterocyclyl, thiol, alkylthio, arylthio, alkylthioalkyl, arylthioalkyl, alkylsulfonyl, alkylsulfonylalkyl, arylsulfonylalkyl, alkoxy, aryloxy, aralkoxy, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aryloxycarbonyl, haloalkyl, amino, trifluoromethyl, cyano, nitro, alkylamino, arylamino, alkylaminoalkyl, arylaminoalkyl, aminoalkylamino, hydroxy, alkoxyalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, acyl, aralkoxycarbonyl, carboxylic acid, sulfonic acid, sulfonyl, phosphonic acid, heteroaryl, heterocyclic, and aliphatic."

As is evident from their structural definition, the compounds according to claim 1 are based on the N-acyloxymethyl substructure N-CHA-O(C=O) where N is the δ-lactam nitrogen atom, CHA-O(C=O) is part of R_5 and A is either hydrogen or one of the substituents R_{10}, R_{105}, Me, Et, *i*-Pr or (C=O)OMe. The substituent R_5 in formula V, therefore, is referred to in the following as being an acyloxymethyl substituent.

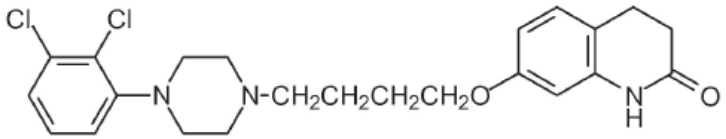
2. Clarity (Article 84 EPC) and amendments (Article 123(2) and (3) EPC)

The board is satisfied that the amendments in claim 1 meet the requirements of Articles 84 and 123(2) and (3) EPC.

3. Inventive step (Article 56 EPC)

3.1 In the decision under appeal, either of documents D37 or D43 were taken as the starting point for the assessment of inventive step.

Both D37 (example 1) and D43 (page 1, paragraphs 1 and 2) disclose the antipsychotic drug aripiprazole, i.e. the following compound:



In view of its structural similarity to the compounds of claim 1, the appellant considered these disclosures to represent the closest prior art. The board sees no reason to take a different stance.

3.2 The subject-matter of claim 1 is distinguished from aripiprazole in that the compounds of formula V bear the acyloxymethyl substituent R_5 on the δ-lactam nitrogen atom instead of a hydrogen atom.

3.3 The experimental data in the patent (table E on page 118) show for 18 different compounds according to claim 1, without a double bond in conjugation with the δ-lactam carboxyl group, that *in vivo,* the acyloxymethyl substituent R_5 is replaced by a hydrogen atom, thus yielding aripiprazole. In the absence of evidence to the contrary, the board accepts that *in vivo,* compounds according to claim 1 having a double bond in conjugation with the δ-lactam carboxyl group undergo an analogous transformation to dehydro aripiprazole. As shown in D56 (page 23, point 12.3), dehydro aripiprazole has a similar antipsychotic activity to aripiprazole.

Thus, the compounds according to claim 1 are prodrugs of the corresponding antipsychotic parent drugs aripiprazole and dehydro aripiprazole.

The objective technical problem, therefore, is the provision of prodrugs of aripiprazole/dehydro aripiprazole.

3.4 D53 and D58, addressed in relation to obviousness in the decision under appeal and in the appellant's statement of grounds of appeal respectively, look at prodrugs from a structural perspective.

3.4.1 D58 is a review article entitled "*Prodrugs: design and clinical applications*". According to D58 (figure 1), common prodrug strategies for drugs containing a N-H functional group are the formation of amides,

carbamates, N-Mannich bases, oximes, imines and phosphates. However, D58 does not suggest to replace the hydrogen atom in a N-H functional group with an acyloxymethyl substituent, let alone one of the acyloxymethyl substituents R_5 according to claim 1.

3.4.2 D53 is a review article entitled "*Pro-Drugs of Amides, Imides, and Amines*". Although D53 (chapter I.B.) discloses that N-acyloxymethylation can give prodrugs, the N-H functional groups that are provided with an acyloxymethyl group in exchange for their hydrogen atom are part of imide or imidazole moieties and thus entirely different from amide N-H groups, let alone δ-lactam N-H groups. Therefore, the skilled person would not have expected, at least not with a reasonable expectation of success, that the acyloxymethylation of aripiprazole/dehydro aripiprazole, or more precisely, that the replacement of the hydrogen atom bound to the δ-lactam nitrogen atom by the acyloxymethyl groups R_5 would have led to prodrugs of aripiprazole and dehydro aripiprazole.

3.5 It follows that the subject-matter of claim 1 and its dependent claims 2 to 11 involves an inventive step. The reasoning above applies *mutatis mutandis* to the other independent claims 12, 14 and 18 and their dependent claims 13 and 15 to 17 as they ultimately refer back to a compound according to any one of claims 1-11. Consequently, the set of claims of the main request is allowable.

Reimbursement of the appeal fee

4. Pursuant to Rule 103(1)(a) EPC, the appeal fee shall be reimbursed in full where the board deems an appeal to

be allowable, if such reimbursement is equitable by reason of a substantial procedural violation.

4.1 Allowability of the appeal

The set of claims of the main request on appeal is identical to that of the first auxiliary request on which the decision under appeal is based (*supra*, VII). Contrary to the opposition division (*supra*, III), the board considers this set of claims to meet the requirements of the EPC. The appeal, therefore, is allowable.

4.2 Substantial procedural violation

4.2.1 During oral proceedings before the opposition division, the then main request of the decision under appeal was discussed first. After the opposition division announced its negative conclusion on inventive step, the appellant chose not to discuss the first auxiliary request but an even lower ranking auxiliary request. It was however made clear that the first auxiliary request was maintained (minutes, page 1, last paragraph).

According to the decision under appeal (page 5, paragraphs 4 to 7), in the assessment of inventive step, when the variable w is 4, the objective technical problem of providing prodrugs of compounds of formula V had been solved. However, claim 1 of the main request was found to lack inventive step on the basis that claim 1 allowed further values for w (e.g. 0 or 11) for which said problem was not considered solved.

In claim 1 of the then first auxiliary request (present main request), the variable w was limited to 4.

In relation to the first auxiliary request, the decision under appeal merely states (point 8 on page 6):

> "*The proprietor decided to keep the first and second auxiliary request on file but to continue the oral proceedings by discussing the third auxiliary request.*"

4.2.2 Contrary to Rule 111(2) EPC, no reasoning at all was provided in the decision under appeal as to why the first auxiliary request was not considered allowable. This complete lack of reasoning amounts to a substantial procedural violation (Case Law of the Boards of Appeal of the European Patent Office, 9th edition, 2019, V.A.9.5.9).

The mere fact that the first auxiliary request was not discussed during oral proceedings did not relieve the opposition division of its duty to provide reasons in the decision as to why that request was found not to be allowable, and thus from showing that the appellant's arguments regarding this request had duly been taken into account. This is all the more true because it is not readily apparent why the reasoning given for the main request should also apply to the first auxiliary request. On the contrary, as set out above, the decision under appeal explicitly indicates that the objective technical problem was solved when the variable w = 4. The reasoning that claim 1 of the main request did not solve said objective technical problem, and therefore lacked inventive step, consequently cannot apply to claim 1 of the first auxiliary request in which w is limited to 4.

4.3 Equitableness of the reimbursement

With its appeal, the appellant continues to pursue as part of its main request, the set of claims of the first auxiliary request before the opposition division. There is, therefore, a causal link between the substantial procedural violation (i.e. the lack of reasoning in the decision under appeal as regards the first auxiliary request) and the filing of the appeal.

The fact that the appellant itself chose to not discuss the first auxiliary request during the oral proceedings before the opposition division is also not a reason that would make reimbursement of the appeal fee appear inequitable because this conduct served, if anything, to expedite the oral proceedings.

For the above reasons, the reimbursement of the appeal fee is also equitable.

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 in amended form with the following claims and a description to be adapted thereto:

   Claims 1 to 18 of the main request, filed as first auxiliary request with the statement of grounds of appeal

3. The appeal fee is reimbursed.

The Registrar: The Chairman:

M. Schalow P. O'Sullivan

Decision electronically authenticated