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**Datasheet for the decision
of 13 May 2019**

Case Number: T 1393/14 - 3.3.01

Application Number: 07810283.7

Publication Number: 2049101

IPC: A61K31/353, C07D311/58

Language of the proceedings: EN

Title of invention:

SUBSTITUTED 4-ARYL-CHROMENE AS ACTIVATOR OF CASPASES AND
INDUCER OF APOPTOSIS AND AS ANTIVASCULAR AGENT AND THE USE
THEREOF

Applicant:

Cytovia, Inc.

Headword:

Caspase activator/CYTOVIA

Relevant legal provisions:

EPC Art. 56

Keyword:

Inventive step - (no)



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Case Number: T 1393/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 May 2019

Appellant: Cytovia, Inc.
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 22 October 2013
refusing European patent application No.
07810283.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman A. Lindner
Members: J. Molina de Alba
L. Bühler

Summary of Facts and Submissions

- I. By its decision according to the state of the file posted on 22 October 2013, the examining division refused European patent application No. 07 810 283.7.

The decision was based on the set of 19 claims filed on 23 November 2012 and the reasons provided in the communication dated 7 June 2013. In that communication, the examining division considered *inter alia* that the compound in claim 1 was not novel and the compound in claim 3 was not inventive.

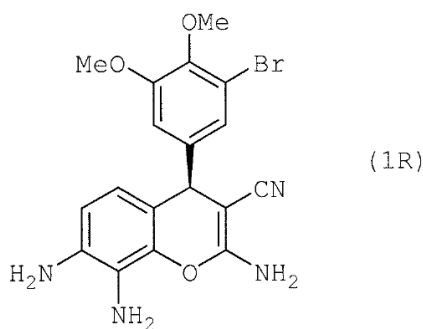
- II. The following documents are referred to in the present decision:

D1: WO 02/092594
D3: L. Miller et al., J. Chromatogr. A, 1999, 865, 211-226
D4: WO 2005/046575
D5: I. Hutchinson et al., J. Med. Chem., 2002, 45, 744-747
D8: C.H. Lochmüller et al., J. Chromatogr., 1975, 113, 283-302
D9: R. Bushan et al., Biomed. Chromatogr., 1998, 12, 309-316

- III. The applicant (appellant) filed an appeal against the decision of the examining division. With its statement of grounds of appeal, the appellant requested that the decision be set aside and a patent be granted on the basis of the claims on which the decision was based (main request). In addition, the appellant filed two sets of claims as auxiliary requests 1 and 2.

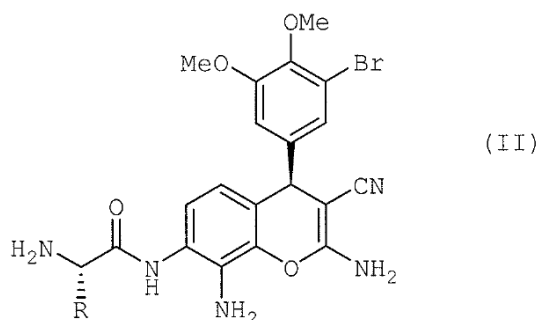
Claims 1 and 3 of the main request read as follows (emphasis in the original):

"1. A compound of Formula **1R**, greater than 95% free from the corresponding (S)-stereoisomer:



or a pharmaceutically acceptable salt thereof."

"3. A compound of Formula **II**:



or a pharmaceutically acceptable salt thereof;

wherein

R is hydrogen, alkyl and alkyl substituted with hydroxy, carboxy, carbamoyl, mercapto, imidazolyl, methylthio, aryl, amino or guanidine; or

R and the NH₂ group that is bonded to the carbon atom to which R is bonded, are taken together to form a ring."

Claims 1 and 3 of auxiliary request 1 are identical to those of the main request.

Claim 1 of auxiliary request 2 is identical to claim 3 of the main request.

- IV. In a communication sent as an annex to the summons to oral proceedings, the board gave its preliminary opinion that, *inter alia*, the compounds of formula (1R) and (II) lacked inventive step.
- V. Oral proceedings were held before the board on 13 May 2019. The appellant was absent, as announced previously with a letter dated 23 April 2019.
- VI. The appellant's arguments, where relevant to the present decision, may be summarised as follows:

The racemic mixture disclosed in example 45 of document D1 (hereafter "the racemate") is the closest prior art.

The subject-matter of claim 1 of the main request is inventive. As shown in Table I of the application, compound (1R) is the active enantiomer of the racemate in relation to the activation of caspases; the other enantiomer has no substantial activity. The technical problem to be solved may then be formulated as the provision of an improved activator of caspases, inducer of apoptosis and antivasular agent.

The solution proposed in claim 1 is inventive because the limited activity of the racemate as caspase activator shown in D1 (see Table I, entry 45) deterred the skilled person from resolving it to select the more active enantiomer.

For the same reason, the subject-matter of claim 3 of the main request is also inventive. Furthermore, the

presence of an additional difference with the closest prior art, namely that compound (1R) is formulated as a prodrug, makes it even more inventive.

- VII. The appellant requested in writing that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims filed on 23 November 2012, which underlies the decision under appeal (main request). Alternatively, the appellant requested that a patent be granted on the basis of any of the sets of claims filed as auxiliary requests 1 and 2 with the statement of grounds of appeal.
- VIII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.
2. The appellant did not attend the oral proceedings before the board, as announced with the letter dated 23 April 2019. In view of this and in accordance with Rule 115(2) EPC and Article 15(3) RPBA, the board maintained the oral proceedings and treated the appellant as relying only on its written case.

Taking into consideration that the facts and evidence on which the present decision is based were known to the appellant from the written proceedings, and that it had sufficient opportunity to present its comments, the board was in a position to announce a decision at the

conclusion of the oral proceedings, in accordance with Article 15(6) RPBA.

3. *Novelty - claim 1 of the main request*

Example 45 of document D1 discloses the preparation of a racemic mixture (the racemate) containing the compound of formula (1R) in claim 1 of the main request and its corresponding enantiomer. The document, however, does not single out either of the two enantiomers comprised in the racemate.

The examining division considered that compound (1R) was anticipated by the racemate because document D1 stated on page 27, paragraph 3, that "*The invention includes all stereoisomers and both the racemic mixtures of such stereoisomers, as well as the individual enantiomers that may be separated according to methods that are well known to those of ordinary skill in the art*".

The board does not agree with this view because the cited passage does not unambiguously single out the enantiomer of formula (1R), as it is uncertain that the blanket statement on page 27, paragraph 3, applies to each and every compound disclosed in document D1. This is reinforced by the fact that all of the biological examples reported in D1 (see pages 91 to 96), without exception, were carried out on racemic mixtures.

Hence, compound (1R) is novel (Article 54 EPC).

4. *Inventive step - claim 1 of the main request*

4.1 The application at hand concerns the use of compound (1R) against cancer, based on its effect as activator

of caspases, inducer of apoptosis and antivasular agent shown in the examples of the application. The invention also extends to the amino acid prodrugs of (1R) defined in claim 3 of the main request as formula (II).

- 4.2 The board concurs with the appellant that the racemate disclosed in example 45 of document D1 constitutes the closest prior art. D1 likewise discloses the effect of the racemate as activator of caspase in human breast cell lines T-47D and ZR-75-1 (see Table I, entry 45).
- 4.3 Having regard to the fact that compound (1R) represents a selection within the enantiomers of the racemate and that both the application and D1 focus on the activation of caspase (see Table I in each of the application and D1), the technical problem to be solved may be formulated as the provision of an improved activator of caspase for use in the treatment of cancer.
- 4.4 The board is satisfied that the solution proposed in claim 1, i.e. compound (1R), solves the problem posed. This is apparent from Table I of the application, which shows that compound (1R) doubles the caspase activation potency of the racemate in human breast cell lines T-47D and ZR-75-1. Thus, while the EC₅₀ of compound (1R) is 21nM for T47D cells and 19nM for ZR-75-1 cells, the corresponding values for the racemate (see entry 1) are 42nM and 35nM, respectively. This is consistent with the lack of practical activity shown by the enantiomer (1S), which has EC₅₀ values of above 2000nM for both cell lines.
- 4.5 Regarding the question of whether or not compound (1R) was an obvious solution to the skilled person, the

board, in its preliminary opinion, drew the applicant's attention to documents D3, D8 and D9. These three documents prove that, at the effective date of the application, it was well known that enantiomers generally had different pharmacological effects and that their separation (e.g. by preparative chromatography using chiral stationary phases) was a standard technique in pharmaceutical research and development in order to isolate the more active enantiomer (see D3, page 211, left-hand column, lines 1-6, and page 212, left-hand column, lines 7-15; D8, page 283, paragraph 1; and D9, page 309, paragraph 1). This was also acknowledged by the appellant in the statement of grounds of appeal (see point 2.4.4).

Thus, starting from the racemate and taking into consideration the general knowledge depicted in documents D3, D8 and D9, the skilled person wanting to prepare a more potent caspase activator would have resolved the racemate as an obvious measure to isolate the enantiomer with the highest caspase activation potency. In this way, they would have arrived at compound (1R) without involving any inventive step.

- 4.6 The appellant argued that, although the skilled person was aware of the fact that sometimes one enantiomer shows activity and the other does not, the fact that the racemate had never been separated before was an indicator that its resolution had not been considered useful by the skilled person. This was so because the racemate exhibited only a moderate activity, as shown in Table I of document D1. Therefore, compound (1R) was not obvious.

The board disagrees. The fact that there is no disclosure in the prior art that the racemate had been

resolved has no bearing on the circumstance that the skilled person knew that one of the two enantiomers of the racemate would be very likely more active than the other and that their separation would, with high probability, provide a compound with a caspase activation potency higher than that of the racemate.

4.7 Consequently, the subject-matter of claim 1 of the main request is not inventive (Article 56 EPC).

5. *Inventive step - claim 1 of auxiliary request 1*

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. Thus, its subject-matter lacks inventive step too.

6. *Inventive step - claim 1 of auxiliary request 2*

6.1 Claim 1 of auxiliary request 2 is directed to a family of compounds of formula (II), which are amino acid prodrugs of compound (1R).

6.2 The racemate disclosed in example 45 of document D1 remains the closest prior art.

6.3 The board agrees with the appellant that the compounds of formula (II) differ from the racemate in that they are amino acid prodrugs of the enantiomer (1R). On this basis, the appellant formulated the technical problem to be solved as the provision of an improved drug.

The board notes, nevertheless, that the compounds of formula (II) do not solve that problem. Table I of the application shows the caspase activation potency in T47D cells of two compounds falling under formula (II), namely compounds 4 and 6. These compounds, however,

exhibit caspase activation potencies lower than the racemate: while the EC₅₀ of the racemate is of 42nM, the EC₅₀ of compounds 4 and 6 is of 52nM and 60nM, respectively. In consequence, the technical problem has to be reformulated in a less ambitious way as the provision of an alternative caspase activator for the treatment of cancer.

6.4 The solution proposed in claim 1, i.e. the amino acid prodrugs of formula (II), is obvious.

As acknowledged by the appellant in the statement of grounds of appeal (see point 2.4.13, last sentence), the formulation of medicaments as prodrugs was known in the art before the effective date of the application. This is also apparent from D1, which suggests examples of prodrugs on page 27, line 30 to page 28, line 15, and from document D4, which states on page 2, lines 11-15, that "*The concept of prodrugs is well known, and there are a number of examples of such prodrugs enumerated in the literature and there are a number of prodrugs available in the market*". In particular, documents D4 (see page 2, lines 16-20) and D5 (see abstract) teach the advantages of formulating active ingredients as amino acid prodrugs and cite a number of preferred amino acids that may be used for that purpose, all of which are encompassed by the amino acid moiety of the compounds of formula (II), possibly with the exceptions of hydroxyproline and tyrosine. Thus, D4 proposes on page 7, line 15 to page 8, line 11, the use of glycine (R=H), proline (R=cycllyl), hydroxyproline (R=hydroxycycllyl), lysine (R=4-aminobutyl), serine (R=hydroxymethyl), threonine (R=1-hydroxyethyl), tyrosine (R=4-hydroxybenzyl), glutamic acid (R=2-carboxyethyl) or aspartic acid (R=carboxymethyl), and D5 focuses on lysine (R=4-aminobutyl) and alanine

(R=methyl). Hence, in view of document D4 or D5, the skilled person looking for alternatives to the racemate would have prepared a prodrug with an amino acid such as glycine, proline, lysine, serine, threonine, tyrosine, glutamic acid, aspartic acid or alanine.

Furthermore, having regard to the skilled person's knowledge that in a racemic mixture, one of the enantiomers, as a rule, is more active than the other, the skilled person would have also contemplated as an obvious measure the preparation of an amino acid prodrug of the more active enantiomer of the racemate. Thereby, they would have arrived at the compounds of formula (II) in an obvious manner.

- 6.5 In this respect, the appellant's argument that the moderate activity of the racemate made it an unsuitable candidate for the separation of its enantiomers remains unconvincing.
7. In conclusion, none of the requests on file fulfils the requirement of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



D. Hampe

A. Lindner

Decision electronically authenticated