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Datasheet for the decision of 20 January 2020

Case Number: T 1966/16 - 3.3.07

Application Number: 09714148.5

Publication Number: 2252328

IPC: A61K47/48

Language of the proceedings: EN

Title of invention:
INTRACELLULAR ENZYME AND RECEPTOR MODULATION

Applicant:
GlaxoSmithKline Intellectual Property Development Limited

Headword:
HDAC Modulators / GLAXOSMITHKLINE

Relevant legal provisions:
EPC Art. 56, 111(1)
RPBA 2020 Art. 11, 12(2)

Keyword:
Inventive step - (yes)
Remittal to the department of first instance - special reasons for remitting the case

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Case Number: T 1966/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 January 2020

Appellant: (Applicant)	GlaxoSmithKline Intellectual Property Development Limited 980 Great West Road Brentford Middlesex TW8 9GS (GB)
Representative:	Fowler, Gavin James GlaxoSmithKline Global Patents (CN925.1) 980 Great West Road Brentford, Middlesex TW8 9GS (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 27 January 2016 refusing European patent application No. 09714148.5 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	P. Schmitz

Summary of Facts and Submissions

I. The appeal was filed by the appellant (applicant) against the decision of the examining division to refuse the European patent application No 09714148.5 (hereinafter "the application").

II. The decision was based on a single request with claims 1-7 filed by letter dated 24 February 2015.

Claim 1 read as follows:

"A covalent conjugate of an α,α-disubstituted glycine ester and a modulator of the activity of the target intracellular enzyme histone deacetylase, wherein:

the ester group of the conjugate is hydrolysable by cells containing the intracellular carboxylesterase enzyme hCE-1 to the corresponding alpha amino acid and not hydrolysable by cells containing hCE-2 or hCE-3 but not hCE-1;

the α,α-disubstituted glycine ester is conjugated to the modulator at a position remote from the binding interface between the modulator and the target enzyme histone deacetylase; and

the said α,α-disubstituted glycine ester being conjugated to the modulator via its α-amino group such that the nitrogen of the said amino is not directly linked to a carbonyl moiety,

wherein the position of conjugation is remote when the conjugate has a potency in a cellular activity assay at least as high as that of the unconjugated modulator in the same assay, which cellular activity assay is a cell

proliferation inhibition assay carried out in U937 cancer cells."

III. The decision under appeal cited *inter alia* the following document:

D6: WO 2006/117567 A2

IV. The examining division decided that the claimed subject-matter did not meet the requirements of Article 56 EPC:

The closest prior art D6 disclosed conjugates of an α-amino acid ester and a modulator of histone deacetylase (hereinafter HDAC). The claimed subject-matter differed in that α,α-disubstituted glycines were used. This difference was not shown to result in any technical effect. The problem was formulated as the provision of alternative esterase-sensitive motifs for the conjugates of D6. The selected α,α-disubstituted glycine derivatives represented a subset of the amino acids used in D6, and comprised the essential features described to ensure macrophage selectivity. Hence, the skilled person would have considered modifying the conjugates of D6 and would have obtained the claimed conjugates without the use of any inventive skills.

V. With the statement of grounds of appeal, the appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1-7 filed by letter dated 24 February 2015.

VI. The Board summoned the appellant to oral proceedings.

In a communication pursuant to Article 15(1) RPBA issued on 29 October 2019, the Board expressed the

preliminary opinion that the objection of lack of inventive step laid out in the decision under appeal was not justified. However, the Board expressed doubts as to the compliance of claims 1-7 with the requirements of Articles 83, 84 and 123(2) EPC. Accordingly, the Board could not accede to the appellant's request that a patent be granted on present claims 1-7, but envisaged setting aside the decision under appeal and remitting the case to the examining division for further prosecution.

VII. By letter dated 13 December 2019, the appellant requested as a main request that the decision under appeal be set aside and the application be remitted to the examining division.

The oral proceedings were cancelled.

VIII. The appellant's arguments can be summarised as follows:

The closest prior art D6 disclosed conjugates comprising a modulator of a target intracellular enzyme and an amino acid ester. The only conjugates exemplified in D6 had a mono-substituted ester moiety.

The α,α-disubstituted glycine esters of the present application were neither disclosed in D6 nor were a subgroup of the α-amino acids taught by D6.

The objective technical problem was the provision of alternative compounds that accumulate in the cell and show macrophage selectivity.

The claimed solution, consisting in attaching an α,α-disubstituted glycine ester to the HDAC modulator, was not obvious in light of D6, because the use of mono-

substituted esters would have been seen as an essential feature of the invention disclosed in D6, because common general knowledge would have led the skilled person away from the present invention, and because studies into the ability of different esterases to hydrolyse α,α-disubstituted glycine esters would have confirmed to the skilled person that the addition of a second substituent to the glycine ester moiety would significantly impact hydrolysis.

Reasons for the Decision

1. Inventive step, claim 1

1.1 The present application relates to covalent conjugates comprising an HDAC modulator and an α,α-disubstituted glycine ester. The addition of the α,α-disubstituted glycine ester increases the potency of the HDAC modulator through the following mechanism: hydrolysis of the ester within the cell by intracellular carboxyl esterases creates a charged species that is not readily transported out of the cell, thus leading to an intracellular accumulation of the modulator and hence an increase in cellular potency and duration of action (see e.g. page 2 of the description).

1.2 The closest prior art D6 describes covalent conjugates of an α-amino acid ester and a modulator of the activity of a target intracellular enzyme or receptor, such as HDAC (see claim 1 and example 1). The examples of D6 are α-monosubstituted glycine ester conjugates.

1.3 D6 does not disclose α,α-disubstituted glycine ester conjugates.

1.4 It is not demonstrated that the claimed α,α-disubstituted glycine ester conjugates achieve any additional technical effect in comparison with the α-monosubstituted glycine ester conjugates of D6.

Accordingly, the objective technical problem is the provision of alternative HDAC modulators that accumulate in the cell.

The data in the application (see examples 7 and 9 on pages 58-59) suggest that some conjugates as defined by present claim 1 solve the above problem. At any rate, only those conjugates which solve this problem fall under the scope of claim 1, because the compounds of claim 1 are functionally defined *inter alia* by their ability to be hydrolysed and therefore to accumulate in cells.

1.5 In the Board's view, and contrary to the opinion of the examining division, D6 does not make it credible that α,α-disubstituted glycine esters would be hydrolysed and lead to an accumulation of the HDAC modulator in cells.

α,α-disubstituted glycine esters may formally be encompassed by the expression "alpha amino acid ester" used in claim 1 of D6. However, the skilled person would not infer therefrom that α,α-disubstituted glycine esters are susceptible to hydrolysis, because the disclosure of D6 as a whole rather supports that the intended meaning of "alpha amino acid ester" was α-monosubstituted amino acid. This is for instance apparent from the formula shown on page 11 (lines 10-11) or from the singular expression "the side chain" of the amino acid, used throughout D6.

Furthermore, the Board shares the appellant's view that there was no expectation that α,α-disubstituted glycine esters would be hydrolysable by carboxyl esterases at the priority date of the application. No common general knowledge existed regarding the impact of a second α-substituent on the ease of hydrolysis of the amino acid ester. The statement on page 12 of D6 ("the selection of the side chain group R_2 can determine the rate of hydrolysis") merely emphasizes the influence of the structure of the single α-substituent on ease of hydrolysis, and neither discloses nor provides any incentive to investigate the influence of a second α-substituent.

Consequently, the skilled person faced with the above technical problem could not, on the basis of D6, anticipate that α,α-disubstituted glycine ester conjugates would retain the ability to be hydrolysed by intracellular carboxyl esterases and accumulate in cells.

Accordingly, the finding of lack of inventive step over D6 must be set aside.

2. Remittal to the examining division

2.1 It follows from the above that the sole ground for the refusal set out in the decision under appeal, namely a lack of inventive step over D6, is not justified.

However the Board identified several potential deficiencies in present claims 1-7 with respect to Articles 83, 84 and 123(2) EPC, as explained in the communication of the Board pursuant to Article 15(1) RPBA (see paragraph 2. of the communication dated 29 October 2019). Although the examining division

raised related objections of lack of clarity and sufficiency of disclosure in the communication dated 9 May 2014, the decision under appeal does not address these issues. It is unclear whether the examining division regarded the objections as overcome.

2.2 Under Article 111(1) EPC, the Board may in the present case either proceed further with the examination of the application, in particular with respect to Articles 83, 84 and 123(2) EPC, or remit the case to the examining division for further prosecution.

Since the present appeal was pending on 1 January 2020, the revised version of the RPBA applies (OJ EPO 2019, A63), subject to the transitional provisions set out in Article 25 of said RPBA. In particular Article 11 RPBA 2020 is applicable. Article 11 RPBA 2020 provides that the Board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so.

The Board holds that such special reasons are apparent in the present case because the examining division has not taken an appealable decision on essential outstanding issues with respect to Articles 83, 84 and 123(2) EPC. As recalled in Article 12(2) RPBA 2020, the primary object of the appeal proceedings is to review the decision under appeal in a judicial manner. This principle would not be respected if the Board were to conduct a complete examination of the application. Consequently, in the present case, Article 11 RPBA 2020 does not entail that the board should carry out a full examination of the application for compliance with the requirements of Articles 83, 84 and 123(2) EPC for which no decision of the first instance exists yet.

Under these circumstances, the Board considers it appropriate to allow the appellant's request for remittal of the case to the examining division.

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 for further prosecution.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated