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**Datasheet for the decision  
of 11 February 2019**

**Case Number:** T 2658/16 - 3.3.07

**Application Number:** 08075301.5

**Publication Number:** 1964578

**IPC:** A61K47/48

**Language of the proceedings:** EN

**Title of invention:**

ALPHA AMINOACID ESTER-DRUG CONJUGATES HYDROLYSABLE BY  
CARBOXYLESTERASE

**Applicant:**

GlaxoSmithKline Intellectual Property Development  
Limited

**Headword:**

ALPHA AMINOACID ESTER-DRUG CONJUGATES HYDROLYSABLE BY  
CARBOXYLESTERASE/GlaxoSmithKline Intellectual Property  
Development Limited

**Relevant legal provisions:**

EPC Art. 84

**Keyword:**

All requests - Unclear functional feature

**Decisions cited:**

**Catchword:**



**Beschwerdekammern**  
**Boards of Appeal**  
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Case Number: T 2658/16 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 11 February 2019**

**Appellant:** GlaxoSmithKline Intellectual Property  
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**Representative:** Fowler, Gavin James  
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**Decision under appeal:** **Decision of the Examining Division of the  
European Patent Office posted on 1 July 2016  
refusing European patent application No.  
08075301.5 pursuant to Article 97(2) EPC.**

**Composition of the Board:**

**Chairman** J. Riolo  
**Members:** D. Boulois  
P. Schmitz

## Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division to refuse European patent application n°08075301.5. The decision was based on 14 sets of claims filed with letter of 23 March 2016 as main request and auxiliary requests 1-6, with letter of 31 March 2016 as auxiliary requests 8-12 and with letter of 20 April 2016 as auxiliary request 13.

Claim 1 of the main request read as follows:

"1. A covalent conjugate of an alpha amino acid ester and a modulator of the activity of a target intracellular enzyme or receptor for use in a method of treatment of the human or animal body by therapy, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid;

the nitrogen of the amino group of the amino acid ester is not linked directly to a carbonyl moiety, or left unsubstituted; and

the alpha amino acid ester is conjugated to the modulator at a position remote from the binding interface between the modulator and the target intracellular enzyme or receptor, 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."

- II. According to the decision under appeal, the main request did not meet the requirements of Articles 83 and 84 EPC:
- It was considered to be an undue burden to randomly screen undefined compounds for the claimed activity of "modulator of the activity of a target intracellular enzyme or receptor" in claim 1, contrary to the requirements of Articles 83 and 84 EPC.
  - The selectivity for the intracellular carboxylesterase was seen as a feature essential to the definition of the invention and was missing from claim 1, contrary to the requirements of Article 84 EPC.
  - The feature "wherein the ester group of the conjugate is hydrolysable by" in claim 1 was considered unclear since leaving the reader in doubt as to which of the ester functions in the conjugate it referred to, contravening the requirements of Article 84 EPC.
  - The particular cell proliferation inhibition assay of claim 1 which qualifies the claimed conjugate, namely "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" could not be used for the characterization of a generic conjugate comprising any modulator, leading to an inconsistency and an unclarity in claim 1, contrary to the requirements of Article 84 EPC.

The same applied to auxiliary requests 1 to 12.

- III. The applicant (herein after the appellant) filed an appeal against that decision. With the statement setting out the grounds of appeal dated 31 October 2016, the appellant submitted a main request, and auxiliary requests 1-8, wherein the main request and

auxiliary requests 1-5 corresponded respectively to former auxiliary requests 8-13 filed in the examination proceedings, and auxiliary requests 6-8 corresponded respectively to former auxiliary requests 8, 9 and 13 with some minor amendments.

Claim 1 of the main request (corresponding to former auxiliary request 8) read thus as follows:

"1. A covalent conjugate of an alpha amino acid ester and a modulator of the activity of a target intracellular enzyme or receptor for use in a method of treatment of the human or animal body by therapy, wherein:

the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid, wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells;

the nitrogen of the amino group of the amino acid ester is not linked directly to a carbonyl moiety, or left unsubstituted; and

the alpha amino acid ester is conjugated to the modulator at a position remote from the binding interface between the modulator and the target intracellular enzyme or receptor, 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."

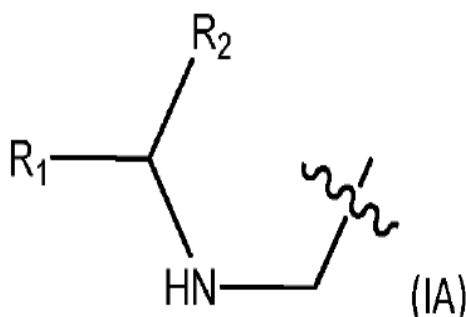
Claim 1 of auxiliary requests 1-8 read as follows, difference with claim 1 of the main request filed in

the appeal proceedings put in evidence (bold or striked out):

a) Auxiliary request 1

Claim 1 of this request corresponds to claim 1 of the main request, with the further specification:

**"the alpha amino acid ester is conjugated to the modulator as a radical of formula (IA):**



wherein R1 is an ester group which is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group, and R2 is the side chain of a natural or non-natural alpha amino acid;".

b) Auxiliary request 2

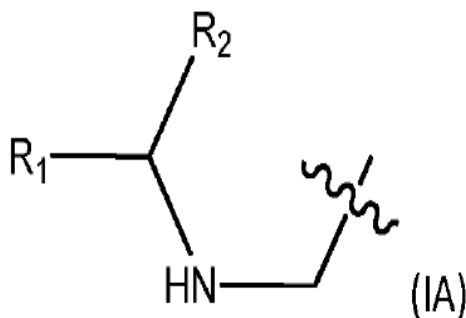
Claim 1 of auxiliary request 2 has been reformulated as "A method of selectively increasing or prolonging, in macrophage and monocyte cells relative to other cell types, the intracellular potency and/or residence time of a modulator of the activity of a target intracellular enzyme or receptor comprising structural modification of the modulator by covalent attachment thereto of an alpha amino acid ester, wherein:...".

c) Auxiliary request 3

Claim 1 of this request corresponds to claim 1 of auxiliary request 2, with the further specification: "the ester group of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid, **wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells;**"

d) Auxiliary request 4

Claim 1 of this request corresponds to claim 1 of auxiliary request 3, with the further specification: "**the alpha amino acid ester is conjugated to the modulator as a radical of formula (IA):**"



**wherein R1 is an ester group which is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group, and R2 is the side chain of a natural or non-natural alpha amino acid;**".

e) Auxiliary request 5

In comparison to claim 1 of the main request, claim 1 of auxiliary request 5 has been restricted to "A covalent conjugate of an alpha amino acid ester and **an inhibitor of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis wherein...**".



f) Auxiliary request 6

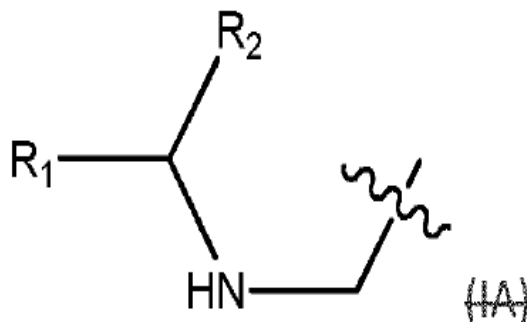
Claim 1 of this request has been further specified by the following restriction:

**"the alpha amino acid ester of the conjugate is hydrolysable by the intracellular carboxylesterase enzyme hCE-1 ~~one or more intracellular carboxylesterase enzymes~~ to the corresponding acid, wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells;**

b) Auxiliary request 7

Claim 1 of this request has been further specified by the following restriction:

"the alpha amino acid ester is conjugated to the modulator as a radical of formula:



**wherein R1 is an ester group ~~which is hydrolysable by one or more intracellular carboxylesterase enzymes to a carboxylic acid group~~ and R2 is the side chain of a natural or non-natural alpha amino acid;**

the **alpha amino acid** ester group of the conjugate is hydrolysable by ~~one or more~~ **the** intracellular carboxylesterase enzyme **hCE-1** to the corresponding

acid, wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells;".

c) Auxiliary request 8

Claim 1 of this request has been restricted by the following features:

"1. A covalent conjugate of an alpha amino acid ester and an inhibitor of the activity of a target intracellular enzyme or receptor **for use in a method of treating rheumatoid arthritis** wherein: the alpha amino acid ester group of the conjugate is hydrolysable by ~~one or more~~ **the** intracellular carboxylesterase enzyme **hCE-1** to the corresponding acid, wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells;..."

- IV. A communication expressing the board's preliminary opinion was sent to the appellant. It stated in particular that none of the requests met inter alia the requirements of Article 84 EPC.
- V. Oral proceedings before the board of appeal took place on 11 February 2019.
- VI. The appellant's arguments can be summarised as follows:

The feature "a modulator of the activity of a target intracellular enzyme or receptor" in claim 1 of the main request was clear, since a skilled person would start with a known "modulator", with a known structure, and known to interact with a receptor or enzyme that is located intracellularly. The invention is not concerned with the identification of new "modulators", but is a new concept with general applicability that relies on

conjugation of a known parental modulator to an alpha amino acid ester.

The invention lay in a new delivery system which was applicable to any "modulator", which was not an essential element of the claimed invention. There were three requirements as regards the delivery system:

- the amino acid ester had to be hydrolysable,
- the amino acid ester had to be bound by the nitrogen of the amino group of the amino acid,
- the amino acid ester had to be bound at a remote position.

This delivery system allowed a selectivity of the action, irrespectively of the type of the modulator to be released. The description of the application showed three different modulators attached to the amino acid ester as claimed, said three modulators having a different structure and activity, namely compounds (5), (8) and (24).

This argumentation was valid for all requests.

Moreover, claim 1 of auxiliary requests 2 to 4 was amended to a method of selectively increasing or prolonging, the intracellular potency or residence of a modulator. This method relegates the modulator to a secondary importance, since there was no method of screening necessary anymore to determine the nature of the modulator.

Claim 1 of auxiliary request 5 was restricted to "an inhibitor of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis". The scope of the modulator was significantly limited to an "inhibitor" type and for selectively treating rheumatoid arthritis.

The same argumentation applied to auxiliary request 8 which was limited to "a modulator of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis".

#### VII. Requests

The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the sets of claims of the main request or one of auxiliary requests 1 to 8 filed with the statement setting out the grounds of appeal.

### **Reasons for the Decision**

#### 1. Main Request - Article 84 EPC

Claim 1 of the main request relates mainly to "a covalent conjugate of an alpha amino acid ester and a modulator of the activity of a target intracellular enzyme or receptor", wherein *inter alia* "the alpha amino acid ester is conjugated via the amino group of the alpha amino acid ester" and "the nitrogen of the amino group of the amino acid ester is not linked directly to a carbonyl moiety".

Said conjugate is further defined by the following features:

- "the ester of the conjugate is hydrolysable by one or more intracellular carboxylesterase enzymes to the corresponding acid, wherein the corresponding acid is capable of selectively accumulating in hCE-1 expressing cells", and

- "the alpha amino acid is conjugated to the modulator...at a position remote from the binding interface between the modulator and the target intracellular enzyme or receptor and 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".

- 1.1 One of the components of the claimed conjugate is thus "a modulator of the activity of a target intracellular enzyme or receptor", and is defined in the form of a functional feature.

Although functional features are generally allowable, a functional feature must remain clear in the sense that the person skilled in the art with his common general knowledge in reading the claim, must be able to understand what is meant by the claim without ambiguity and without complicated, time-consuming investigations, i.e. without undue burden, and must be able to derive a clear definition of what is intended to be claimed. Said features must provide instructions which are sufficiently clear for the skilled person to reduce them to practice without undue burden. This is not the case with the functional feature "a modulator of the activity of a target intracellular enzyme or receptor".

Said feature is indeed vague and unclear and comprises potentially an undefined and great number of possible variables. The claimed modulator does not contain any restriction as to the activity and target, and does not help in identifying which compounds are intended to be used as modulators and a skilled person does not know

to which structural feature or features it corresponds. This feature as such is so vague and ambiguous that it relates to a vast catalogue of possible derivatives of unspecified structure.

Since the technical feature "a modulator of the activity of a target intracellular enzyme or receptor" is unclear for the reasons given above, it prevents the skilled person from identifying the exact meaning thereof, and the public is left in doubts as to the distinction of which "modulators" are covered by claim 1 and which are not, which is at variance with the principle of legal certainty.

For this reason, the area covered by the claim is not clearly defined.

- 1.2 The appellant argued that said feature "a modulator of the activity of a target intracellular enzyme or receptor" was not an essential element of the invention, which was instead the modulator delivery system, i.e. the amino acid ester and the conjugation link, or even the conjugation link between the amino acid ester and the modulator. Moreover, three different compounds were disclosed in the description, which showed that the skilled person could identify potential modulators.

The Board could not follow the appellant's arguments for the following reasons.

- 1.2.1 First of all, the assessment of clarity of a claim cannot be limited to some of its features, presented objectively or subjectively as the essential elements of the claimed invention. All features present in a claim must meet the requirements of Article 84 EPC.

- 1.2.2 In the present case, claim 1 of the main request is furthermore not restricted to the delivery system or the conjugation link and comprises further features relating *inter alia* to the conjugated modulator. The remaining features considered as non-essential by the appellant must also be taken in account for the assessment of the further requirements of the EPC, such as novelty or inventive step. If the core of the invention was indeed the modulator delivery system or the conjugation link, the applicant had the possibility of limiting the subject matter of the claim to that particular subject matter, with the consequence that said limited subject-matter has also to be assessed as such as regards the remaining requirements of the EPC, such as *inter alia* novelty and inventive step.
- 1.2.3 Moreover, the disclosure of three compounds in the description of the patent application, namely compounds (5), (8) and (24), having a different structure and a different activity is irrelevant to the question of clarity of the claimed feature.

Claim 1 relates mainly very broadly to a conjugate between an alpha amino ester and a modulator, wherein the nitrogen of the amino group of the amino acid ester is not directly linked to a carbonyl moiety; this combination encompasses potentially a great number of possible compounds. The question as regards the clarity of the feature relating to the modulator does not boil down to whether some compounds disclosed in the description fall under the claimed definition, but rather to determine whether an existing compound would fall under said claimed definition. This amounts to forcing a person skilled in the art to check whether any compound conjugated to an amino acid ester could

have any kind of modulation activity on any kind of intracellular enzyme or receptor. In the absence of any specification of structure or activity in the claim, this amounts to undue burden, which is contrary to the requirements of clarity.

- 1.3 The subject-matter of claim 1 is therefore unclear in view of the feature "a modulator of the activity of a target intracellular enzyme or receptor". In view of this conclusion, the Board does not see any need in analyzing the clarity of the further remaining functional features in claim 1 of the main request.

Consequently, the main request does not meet the requirements of Article 84 EPC.

2. Auxiliary request 1 - Article 84 EPC

The feature "a modulator of the activity of a target intracellular enzyme or receptor" is also present in claim 1 of auxiliary request 1, which leads to the same conclusions as for the main request and thus auxiliary request 1 does not meet the requirements of Article 84 EPC.

3. Auxiliary request 2 - Article 84 EPC

The feature "a modulator of the activity of a target intracellular enzyme or receptor" is present in claim 1 of auxiliary request 2, and the conclusions as to lack of clarity reached for the main request apply also to this request.

The fact that claim 1 has been reformulated as "a method of selectively increasing or prolonging, in macrophage and monocyte cells relative to other cell



types, the intracellular potency and/or residence time of a modulator of the activity of a target intracellular enzyme or receptor" cannot have any incidence on the lack of clarity stated above. The skilled person is still in a position not enabling him to identify which compounds are intended to be used as modulators and a skilled person does not know to which structural feature or features it corresponds.

4. Auxiliary request 3 - Article 84 EPC

As in auxiliary request 2, claim 1 has been reformulated as "a method of selectively increasing or prolonging, in macrophage and monocyte cells relative to other cell types, the intracellular potency and/or residence time of a modulator of the activity of a target intracellular enzyme or receptor".

The conclusions stated above for auxiliary request 2 and the main request apply *mutatis mutandis* to this request, in view of the feature "a modulator of the activity of a target intracellular enzyme or receptor" in claim 1 and auxiliary request 3 does not meet the requirements of Article 84 EPC.

5. Auxiliary request 4 - Article 84 EPC

As in auxiliary requests 2 and 3, claim 1 of auxiliary request 4 has been reformulated as "a method of selectively increasing or prolonging, in macrophage and monocyte cells relative to other cell types, the intracellular potency and/or residence time of a modulator of the activity of a target intracellular enzyme or receptor". The same conclusions apply *mutatis mutandis* to this request, in view of the feature of the

feature "a modulator of the activity of a target intracellular enzyme or receptor" in claim 1.

Consequently, auxiliary request 4 does not meet the requirements of Article 84 EPC.

6. Auxiliary request 5 - Article 84 EPC

Claim 1 relates to a conjugate comprising "an inhibitor of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis".

The restriction to an "inhibitor" instead of a more general "modulator" claimed modulator does still not allow to identify which compounds are intended to be used as inhibitors or which enzyme or receptor has to be inhibited, and a skilled person does not know to which structural feature or features it corresponds. This feature remains so vague and ambiguous that it relates to a vast catalogue of possible derivatives of unspecified structure.

Moreover, the further restriction to the "use in a method of treating rheumatoid arthritis" necessitates a further identification and research work as to the medical use of the claimed unidentified inhibitor.

The skilled person is therefore still unable to establish without undue burden which compounds might fall under the double limitation "an inhibitor of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis".

Consequently, auxiliary request 5 does not meet the requirements of Article 84 EPC.

7. Auxiliary requests 6 and 7 - Article 84 EPC

Claim 1 of auxiliary requests 6 and 7 relate to "a modulator of the activity of a target intracellular enzyme or receptor" and lacks clarity for the same reason as the main request.

Consequently, they do not meet the requirements of Article 84 EPC.

8. Auxiliary request 8 - Article 84 EPC

As in auxiliary request 5, claim 1 of this request relates to a conjugate comprising "an inhibitor of the activity of a target intracellular enzyme or receptor for use in a method of treating rheumatoid arthritis".

The conclusions reached for auxiliary request 5 apply *mutatis mutandis* to auxiliary request 8, which does not meet the requirements of Article 84 EPC.

**Order**

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar:

The Chairman:



K. Götz-Wein

J. Riolo

Decision electronically authenticated