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Datasheet for the decision of 15 April 2008

Case Number: T 1844/07 - 3.3.02

Application Number: 98963173.4

Publication Number: 1037649

IPC: A61K 47/48

Language of the proceedings: EN

Title of invention:
Polymeric prodrugs of amino- and hydroxly-containing bioactive agents

Applicant:
ENZON, INC.

Opponent:
-

Headword:
PEG double prodrugs/ENZON

Relevant legal provisions:
EPC Art. 123(2), 84, 111(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Restricted set of claims filed at appeal proceedings is allowable"
"Remittal"

Decisions cited:
-

Catchword:
-

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Case Number: T 1844/07 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 15 April 2008

Appellant: (Applicant)
ENZON, INC.
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Representative:
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Decision under appeal:
Decision of the Examining Division of the European Patent Office posted 17 April 2007 refusing European application No. 98963173.4 pursuant to Article 97(1) EPC 1973.

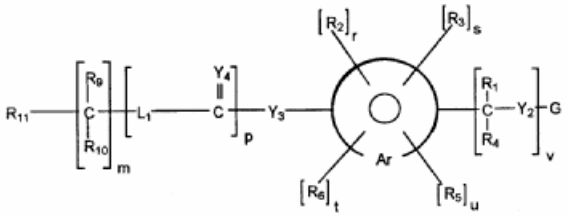
Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
J.-P. Seitz

Summary of Facts and Submissions

I. European patent application No.98 963 173.4 based on international patent application WO 99/30727 was filed with 33 claims. Claim 1 read as follows:

1. A compound comprising the formula:

(I) 

wherein:

L_1 is a bifunctional linking moiety;

G is H or $-\overset{Y_1}{\overset{\|}{C}}-B$; where

B is H, a leaving group, a residue of an amine-containing moiety, or a residue of a hydroxyl-containing moiety;

Y_{1-4} are independently O, S, or NR_{12};

R_1, R_4, R_9, R_{10}, and R_{12}, are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkyl carbonyls;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

(m), (r), (s), (t), (u) and (v) are independently zero or one;

(p) is zero or a positive integer; and

R_{11} is a substantially non-antigenic polymer.

II. The following documents have been cited *inter alia* during the examination and appeal proceedings:

(3) R.B. Greenwald, Expert Opinion on Therapeutic Patents, 1997, 7(6), 601-609

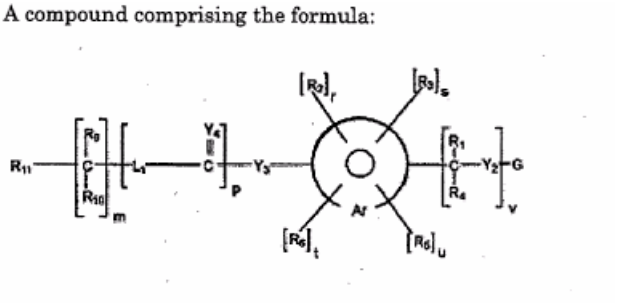
(5) H. Bundgaard, Advanced Drug Delivery Reviews, 1989, 3, 39-65.

III. The appeal lies from the decision of the examining division refusing the patent application under Article 97(1) EPC 1973 pursuant to the requirements of Article 56 EPC.

IV. The examining division considered that the set of claims filed during the oral proceedings before the examining division (main and sole request before the examining division) lacked an inventive step. The examining division identified document (3) as closest prior art, which was combined with document (5) in the reasons given for lack of inventive step.

Claim 1 of the request before the examining division read as follows:

1. A compound comprising the formula:



(I)

wherein:

L_1 is a bifunctional linking moiety;

G is $-C(=Y_1)-B$; where

B is H, a leaving group, a residue of an amine-containing moiety, or a residue of a hydroxyl-containing moiety;

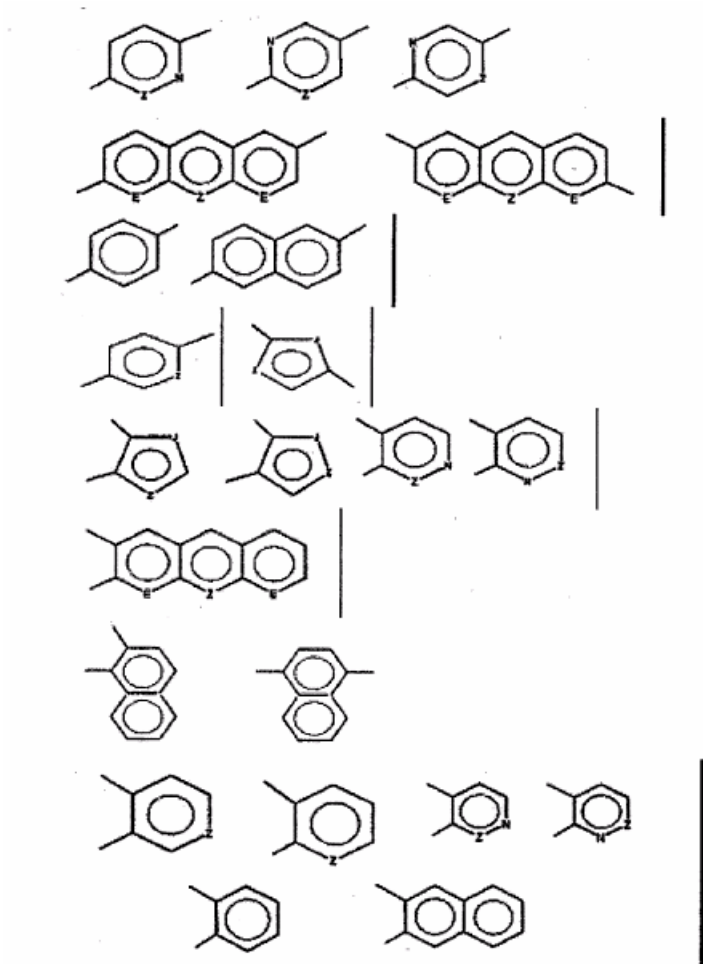
Y_{1-4} are independently O, S, or NR_{12};

R_1, R_4, R_9, R_{10}, and R_{12} are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls;

R_2, R_3, R_5 and R_6 are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{1-6} alkoxy, phenoxy, C_{1-8} heteroalkyls, C_{1-8} heteroalkoxy, substituted C_{1-6} alkyls, C_{3-8} cycloalkyls, C_{3-8} substituted cycloalkyls, aryls, substituted aryls, aralkyls, halo-, nitro-, cyano-, carboxy-, C_{1-6} carboxyalkyls and C_{1-6} alkyl carbonyls;

~~the bond joining L_1 to $C(=Y_4)$ is a hydrolysable bond~~;

Ar is a moiety which when included in Formula (I) forms a multi-substituted aromatic hydrocarbon or a multi-substituted aromatic heterocyclic group having the Y_3 and $C(R_1)(R_4)$ moieties in a para or ortho arrangement in the same plane and being selected from the group consisting of:



wherein

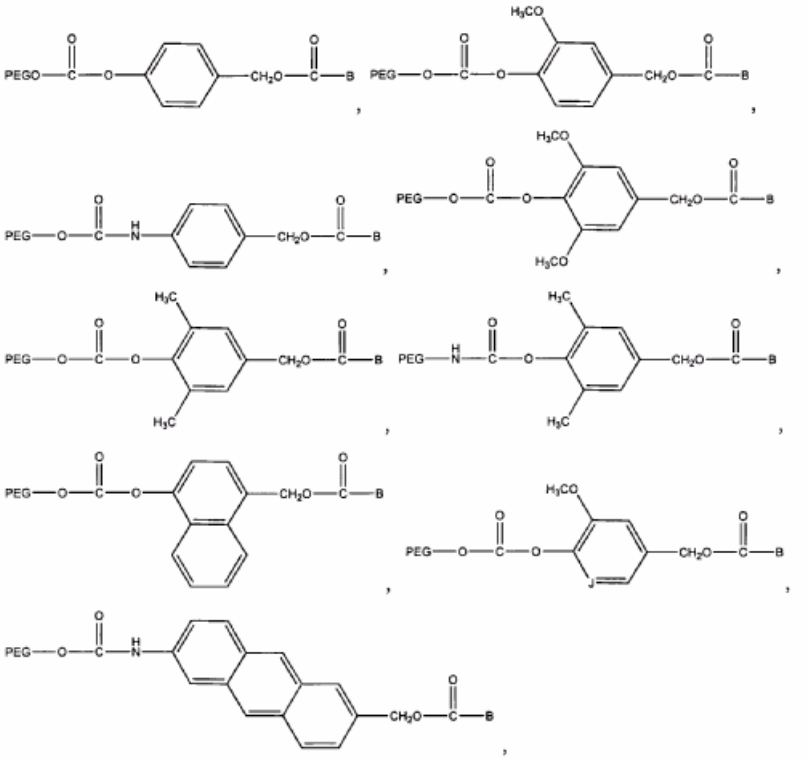
J is O, S, or NR_{13}, E and Z are independently CR_{13} or NR_{13}; and R_{13} is independently selected from the same group as that which defines R_9;
(m), (r), (s), (t), and (u) are independently zero or one;
(v) is one;
(p) is one or a positive integer; and
R_{11} is a non-antigenic polymer which comprises polyalkylene oxide.

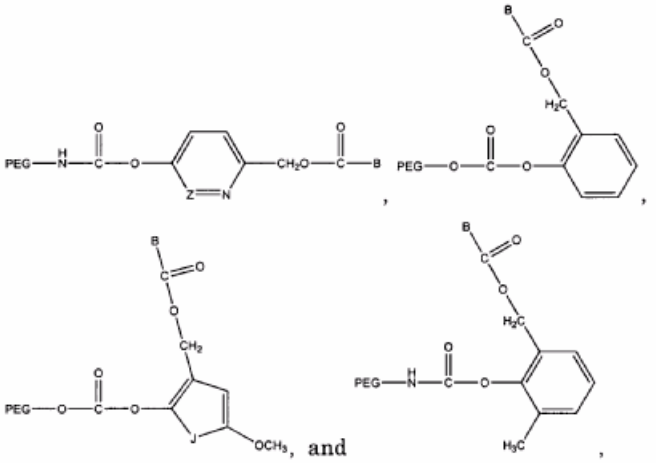
V. The applicant (appellant) lodged an appeal against this decision and filed with its grounds of appeal new sets of claims.

VI. The board sent a communication, as an annex to the summons to oral proceedings, conveying its preliminary opinion in relation to the requirements of Articles 123(2) and 84 EPC.

VII. A new main request and three auxiliary requests were filed with the appellant's reply of 13 March 2008. Claim 1 of the third auxiliary request read as follows:

1. A compound selected from the group consisting of:





wherein

PEG is polyethylene glycol;

B is a residue of an amine-containing moiety or a residue of a hydroxyl-containing moiety linked to C(=O) at the amine or hydroxyl moiety;

J is O, S, or NR_{13};

Z is CR_{13} or NR_{13}; and

R_{13} is independently-selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cycloalkyls, areyls, substituted aryls, aralkyls, C_{1-6} heteroalkyls, and substituted C_{1-6} heteroalkyls.

VIII. Oral proceedings took place on 15 April 2008.
During the oral proceedings the appellant filed a new main request replacing the requests previously on file.

Claim 1 of the main request is identical to claim 1 of the third auxiliary request filed with the letter of 13 March 2008, apart from the correction of the obvious typographical error "areyls" (see definition of R_{13} above) to "aryls".

IX. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows:

The set of claims of the main request differed from the set of claims previously on file as third auxiliary request in the deletion of claims 2 and 5, renumbering

of claims 3, 4, 6, 7 and 8, correction in claim 5 of the reference to a previous claim and avoidance of a redundancy in claim 6.

Claim 1 was based on originally filed claim 28 in which some of the individual formulae were deleted. Moreover, the groups and residues were defined in accordance with claim 1 of the application as filed and the description. Any discrepancies and lack of consistency between the claims and the description were eliminated by modification of the corresponding **passages** of the description pages 5, 20 and 15 to 17.

When asked by the board, the appellant stated that it did not have any objection against a possible remittal to the department of first instance for further prosecution.

X. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request filed during the oral proceedings before the Board of appeal.

Reasons for the Decision

1. *Admissibility*

1.1 The appeal is admissible.

1.2 *Admissibility of the request filed at the oral proceedings before the board*

Claim 1 of the main request filed at the oral proceedings is identical to claim 1 of the third auxiliary request filed with the letter of 13 March 2008, which was filed as response to the board's communication sent as an annex to the summons to oral proceedings. Moreover, the amendments introduced in the main request relate to a fair attempt to overcome in a clear and simple way major problems of clarity and lack of support with respect to the set of claims filed as third auxiliary request with the letter of 13 March 2008.

Therefore, the main request filed at the oral proceedings before the board is admissible.

2. *Article 123(2) and Article 84 EPC*

Claim 1 of the main request is based on claim 28 of the application as originally filed.

The deletion of some of the individual formulae appearing originally in claim 28 of the application as filed does not contravene Article 123(2) EPC since they were independent and separate options for the claimed compound ("a compound selected from the group consisting of").

Claim 28 of the application as filed was dependent on claim 1 of the application as originally filed.

Hence, claim 1 of the main request concerns compounds in which the substantially non-antigenic polymer R_{11}, mentioned in claim 1 as originally filed, is specified as PEG, i.e. polyethylene glycol (PEG is linked as

residue to the rest of the molecule depicted in the formulae).

The description of the application as originally filed discloses definitions for the "water-soluble polymer R_{11}" (pages 15-17), whereby "PEG and its **derivatives**" (emphasis added) appears among the options listed. This means that a difference is clearly made between the commonly known PEG polymer and "PEG's derivatives".

This distinction is further supported by the fact that meanings for R_{11} corresponding to "PEG's derivatives", such as those appearing on pages 15 and 16 of the application as originally filed, are claimed in claim 23 of the application as filed. However, claim 28 of the application as originally filed was not dependent on claim 23.

Therefore, the definition of PEG as polyethylene glycol given in claim 1 of the main request corresponds to the standard chemical meaning given to the term by the skilled person and reflects the normal technical understanding for the expression "PEG" when read as part of the formulae of originally filed claim 28.

Hence, the term PEG employed in claim 1 of the main request is clear and does not extend beyond the content of the originally filed application.

However, in view of the fact that the case is remitted for further prosecution, in order to avoid any inconsistency and lack of clarity (Article 84 EPC) when the department of first instance further considers the (drastically restricted) claim 1 and the definitions

appearing in the description, the appellant was requested by the board to immediately file amended passages of the description corresponding to the polymer residue R_{11}, in accordance with the restricted claim.

The appellant has addressed this issue in a satisfactory manner filing the amended pages 15 to 17. However, the board wishes to point out that no exhaustive adaptation of the description to the amended set of claims has yet taken place.

As regards the definitions of J and Z appearing in claim 1 of the main request, they find a basis at the end of page 9 and top of page 10 of the description as originally filed (together with page 4 for the cross-reference to the definition of R_9).

In relation to the definition of the residue B the following has been considered. Claim 28 of the application as filed was dependent on claim 1 as originally filed. Hence, B, which was the end group linked to the moiety $-C(=Y_1)-$ (wherein Y_1 was inter alia O), was defined as "H, a leaving group or a residue of an amine-containing moiety, or a residue of a hydroxyl-containing moiety".

In claim 1 of the main request B "is a residue of an amine-containing moiety or a residue of a hydroxyl-containing moiety linked to (C=O) at the amine or hydroxyl moiety". This definition of B, although broad, has a clear technical meaning and it clearly covers the cases in which the chemical residues of active agents such as daunorubicin or doxorubicin, enzymes and

proteins (see page 5, lines 9-14 of the application as filed) are linked to the prodrug moiety, but it also includes the residues initially defined as "leaving groups" (page 5, lines 7-8) of the application as filed fulfilling the minimal requirements of this broad definition. In other words, claim 1 of the main request still covers intermediate compounds and end compounds (prodrug derivatives containing the active agent residue). This was also the case of claim 28 as originally filed, the only difference being that the starting materials (B being H) are no longer encompassed by the restricted claim.

Additionally, an investigation of the whole description as filed shows that all the residues B other than H have to be linked to the (C=O) (i.e. Y_1 is O) "at the amine or hydroxyl moiety".

Hence, the definition of B appearing in claim 1 of the main request meets the requirements of Article 84 and 123(2) EPC.

For analogous reasons to those mentioned above for the definition corresponding to the polymer residue R_{11}, it was necessary, in order to avoid any inconsistency (Article 84 EPC), to modify the passages relating to B on pages 5 and 20 of the description. However, as said above, the filing of the amended pages again does not represent an exhaustive adaptation of the description to the restricted claims of the main request.

Hence, the amendments introduced in claim 1 of the main request are allowable (Articles 123(2) and 84 EPC).

Claims 2 to 6 are clear and concise and do not introduce subject-matter extending beyond the content of the application as filed (Articles 84 and 123(2) EPC).

3. The examining division did not object to the novelty of the subject-matter of much broader claims and the board sees no reason to differ.

4. *Remittal*

The decision under appeal refused the patent application on the ground that claim 1 as filed during the oral proceedings before the examining division lacked an inventive step (Article 56 EPC). This claim is reproduced in paragraph IV above.

From a comparison of said claim with claim 1 of the main request, it is self-evident that drastic restrictions in respect of the definition of the prodrug moiety of the compound have been undertaken by the appellant during the appeal proceedings.

Moreover, claim 1 encompasses end compounds, i.e. prodrugs containing the active agent residue, as well as intermediates useful for the preparation of said end compounds. Correspondingly, the intermediate compounds require a separate inventive step analysis to that (to be done) for the end compounds.

Additionally, apart from the identification of the closest prior art, and definition of the problem to be solved, the problem-solution approach also requires other steps to be undertaken before challenging

the obviousness of the subject-matter claimed. These are: identification of the solution as defined in the restricted claim, and examination of whether the problem has been plausibly solved by the claimed solution.

In view of the above, the first instance decision does not hold for the subject-matter claimed in the main request filed at the oral proceedings before the board.

Consequently, the board uses its discretion under Article 111(1) EPC by remitting the case to the department of first instance for further prosecution on the basis of the claims of the appellant's main request filed at the oral proceedings before the board.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the first instance for further prosecution.

The Registrar The Chairman

N. Maslin U. Oswald