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Datasheet for the decision of 23 July 2009

Case Number: W 0028/07 - 3.3.02

Application Number: PCT/EP 2006/069873

Publication Number: WO 2007/071658

IPC: A61K 31/661

Language of the proceedings: EN

Title of invention:
Novel alkyl phosholipid derivatives with reduced cytotoxicity and uses thereof

Applicant:
ÆTERNA ZENTARIS GMBH

Headword:
Alkyl phospholipid derivatives/ÆTERNA ZENTARIS GMBH

Relevant legal provisions:
PCT Art. 17(3)(a)
PCT R. 13, 40.1, 40.2

Relevant legal provisions (EPC 1973):
-

Keyword:
"Lack of unity - (yes): absence of a common technical feature defining a contribution of the claimed Markush grouping over the prior art"

Decisions cited:
W 0018/07, W 0020/07, W 0040/07, W 0003/94

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0028/07 - 3.3.02

International Application No. PCT/EP2006/069873

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 23 July 2009

Applicant: ÆTERNA ZENTARIS GMBH
Weismüllerstrasse 50
D-60314 Frankfurt (DE)

Representative: -

Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 15 May 2007.**

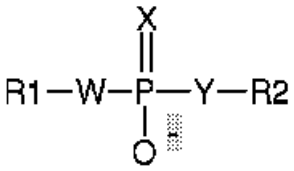
Composition of the Board:

Chairman: H. Kellner
Members: A. Lindner
T. Bokor

Summary of Facts and Submissions

I. The applicant filed an international patent application PCT/EP 2006/069873 comprising a set of 26 claims. Claims 1 and 20 read as follows:

"1. Use of an alkyl phospholipid derivative according to formula (I)



(I),

wherein:
W, X, Y independently are selected from the group consisting of: "oxygen atom, sulphur atom";

R1 is "-$[(CR3R4)_m$-Z$]_n$-R5";

R2 is "-$(CR6R7)_p$-R8";

R3 and R4 are independently from each other selected from the group consisting of "hydrogen atom; substituted or unsubstituted C1-Cl2alkyl, substituted or unsubstituted $(C1\text{-}C12alkyl)_q$-A-$(C1\text{-}Cl8alkyl)_r$, -OH, substituted or unsubstituted -C(O)-(C8-C30alkyl), substituted or unsubstituted -OC(O)-(C8-C30alkyl), substituted or unsubstituted -NHCO-(C1-C12alkyl), substituted or unsubstituted -N(C1-C12alkyl)CO-(C1-C12alkyl)";

or optionally R3 and R4 together form a substituted or unsubstituted saturated, partially unsaturated or aromatic heterocyclic ring system of 3, 4, 5, 6, 7 or 8 ring atoms containing at least one heteroatom selected from the group consisting of: "oxygen atom, sulfur atom";

R5 is independently selected from the group consisting of: "substituted or unsubstituted C8-C30alkyl, substituted or unsubstituted -C(O)-(C8-C30alkyl), substituted or unsubstituted steroid moiety;

R6 and R7 are independently from each other selected from the group consisting of "hydrogen atom, -OH, halogen atom, -F, -Cl, -Br, -I, -CN, C1-C6alkyl, $-CF_3$, $-N_3$, $-NH_2$, $-N0_2$, $-OCF_3$, -SH";

or optionally R6 and R7 together form a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;

or optionally if p is 1, "$-(CR6R7)_p-$" can also be a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms formed together by R6 and R7;

R8 is selected from the group consisting of: "-VR9R10R11; substituted or unsubstituted heterocycle", where heterocycle is

(i) a 5-, 6- or 7-membered saturated, partially unsaturated or aromatic monocyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom,

oxygen atom, sulphur atom, arsenic atom", and with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom, or

(ii) a 7-, 8-, 9-, 10-, 11- or 12-membered saturated, partially unsaturated or aromatic bicyclic carbon atom ring system with at least one heteroatom selected from the group consisting of: "nitrogen atom, oxygen atom, sulphur atom, arsenic atom", and with the proviso that at least one heteroatom is a quaternary nitrogen atom or a quaternary arsenic atom, or

(iii) a tropin moiety,

where two or more ring atoms of heterocycle can be additionally linked via an alkylene-bridge, and where heterocycle if substituted is substituted with at least one radical R12, which in case of two or more radicals R12 are independently from each other identical, partly identical or different;

R9, R10, R11, R12 are independently from each other selected from the group consisting of: "hydrogen atom, substituted or unsubstituted C1-Cl8alkyl, substituted or unsubstituted C3-C8cycloalkyl, substituted or unsubstituted $(C1\text{-}C12alkyl)_s\text{-}B\text{-}(C1\text{-}Cl2alkyl)_t\text{-}C\text{-}(C1\text{-}Cl2alkyl)_u$, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkoxy, -OH, halogen, -F, -Cl, -Br, -I, =O, -C(O)O-(C1-Cl2alkyl), -C(O)O-(C3-C8cyclo-alkyl), -C(O)O-aryl, -C(O)O-heteroaryl, -C(O)O-heterocyclyl, -C(O)-(C1-Cl2alkyl),

-C(O)-(C3-C8cycloalkyl), -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl", and

optionally two substituents R12 can together form a substituted or unsubstituted saturated, partially unsaturated or aromatic ring system of 3, 4, 5, 6 or 7 carbon atoms;

Z is independently selected from the group consisting of "oxygen atom; sulphur atom";

V is independently selected from the group consisting of "nitrogen atom, arsenic atom";

A, B, C are independently from each other selected from the group consisting of "oxygen atom; sulphur atom; $S(O_2)$";

m independently is 1, 2 or 3;

n independently is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 and preferably is 0, 1, 2, or 3;

p independently is 0, 1, 2, 3, 4, 5 or 6, and preferably is 0, 1, 2 or 3;

q, r, s, t, u independently from each other are 0 or 1;

for the manufacture of a medicament for the treatment or prophylaxis of diseases and/or pathophysiological conditions in mammals that are caused by microorganisms.

20. The use of an alkyl phospholipid derivative as claimed in any of claims 1 to 7 for the manufacture of a medicament for the treatment of tumors in mammals."

II. In its communication dated 15 May 2007, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to pay 13 additional search fees.

III. The following documents were *inter alia* cited by the ISA:

(4) M. Koufaki et al., "Alkyl and Alkoxyethyl Antineoplastic Phospholipids"; J. Med. Chem., 1996, vol. 39, no. 13, pp. 2609-2614

(6) WO 03/028736

IV. The ISA defined the treatment of tumours or of a disease or a pathological condition caused by a microorganism selected from the group consisting of a fungus, a protozoon, a bacterium or a virus, as the problem of the present application. The proposed solution to this problem was to use a compound according to formula (I). However, the use of compounds corresponding to formula (I) in relation to the treatment of such disorders was already known in the prior art and could therefore not fulfil the role of a "special technical feature" or of a "general inventive concept" in the sense of Rule 13.2 PCT. Accordingly, there was no new technical effect linking the different groups of inventions. Moreover, the compounds in question did not share a significant structural element,

nor did they belong to a same recognised class of chemical compounds.

The following groups of inventions were identified:

Group 1: claims 1, 2, 5, 7—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 0, and R5 = C8—C30 Alkyl, p = 0 and R8 = has the value given under (i) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 2: claims 1, 2, 5, 7—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 0, and R5 = C8—C30 Alkyl, p = 0 and R8 = has the value given under (ii) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 3: claims 1, 3-5, 7—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 0, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = VR9R1OR11 in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is

selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 4: claims 1, 3-5, 7—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 0, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = has the value given under (i) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 5: claims 1, 3—5, 7—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 0, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = has the value given under (ii) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 6: claims 1, 2, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1—10, and R5 = C8—C30 Alkyl, p = 0 and R8 = VR9R1OR11 in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus,

protozoon, bacterium and or virus, and to treat tumors

Group 7: claims 1, 2, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and R5 = C8—C30 Alkyl, p = 0 and R8 = has the value given under (i) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 8: claims 1, 2, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and R5 = C8—C30 Alkyl, p = 0 and R8 = has the value given under (ii) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 9: claims 1, 3, 4, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = has the value VR9R1OR11 in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group

consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 10: claims 1, 3, 4, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = has the value given under (i) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 11: claims 1, 3, 4, 6—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and R5 = C8—C30 Alkyl, p = 1—10 and R8 = has the value given under (ii) in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 12: claims 1—26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein R8 = is a tropin moiety in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 13: claims 1–26 (partially)

Use of a compound according to formula (I) comprising a quaternary nitrogen atom wherein n = 1, and wherein R5 = is a steroid moiety in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors

Group 14: claims 1–26 (partially)

Use of a compound according to formula (I) comprising a quaternary arsenic atom in relation to the treatment of a disease or a pathophysiological condition caused by a microorganism where the microorganism is selected from the group consisting of fungus, protozoon, bacterium and or virus, and to treat tumors.

V. With his reply dated 15 June 2007, the applicant paid two additional search fees under protest pursuant to Rule 40.2(c) PCT and requested that an additional search be carried out for the groups of inventions 3 and 4.

In support of the protest, the applicant argued that the subject-matter as claimed related to only seven inventions instead of the fourteen inventions as defined by the ISA in the invitation to pay additional search fees: each of the groups of inventions 1-2, 3-5, 6-8, and 9-11 was to be considered as a single group of inventions, as the compounds defined therein had important structural similarities.

In connection with the groups of inventions 3-5, it was held that the compounds of each group had the following common structural features: n = 0;
R1 = R5 = C8-C30-alkyl, p = 1-6 and R2 = R8 = NR9R10R11 or a substituted/unsubstituted heterocycle. In particular, the features p = 1-6 as well as the substituted quaternary nitrogen atom represented the common special technical features of the alleged groups of inventions 3-5. Moreover, the compounds of these three groups were linked by a new technical effect in the form of their antibacterial activity. In addition, the applicant concluded that the extent of the structural similarities of alkylphospholipid derivatives of the present application was such that establishing a written opinion of the ISA did not represent an undue burden.

VI. In the review pursuant to Rule 40.2(c) PCT dated 13 August 2007 the review panel of the ISA came to the conclusion that the invitation to pay additional fees was justified and that, as a consequence, the two additional search fees were not to be refunded. In its argumentation, the review panel essentially held that compounds comprising the commonly shared structure of the subject-matter as defined in the groups of inventions 3 and 4 and comprising an antimicrobial or antitumor activity, had already been disclosed in several prior art documents. As a consequence, the groups of inventions 3 and 4 were not linked by special technical features. In addition, the review panel came to the conclusion that in the present case, the amount of work justified the request for the additional fees.

VII. With the letter of 22 August 2007, the applicant paid the protest fee according to Rule 40.2(e) PCT.

Reasons for the Decision

1. The application in suit was filed on 19 December 2006. Therefore, the protest is subject to the provisions of the PCT in force as from 12 October 2006 including amended Rule 40 PCT. The Boards of Appeal are responsible for deciding on protests relating to PCT applications pending at the time of entry into force of the EPC 2000 (13 December 2007). Details of the procedure are guided by the Decision of the President of the EPO dated 24 June 2007, Article 3 (OJ EPO 2007, Special edition No. 3, 140-141). Reference is also made to decisions W 0018/07, W 0020/07 and W 0040/07 (see points 1.1-1.3 of the reasons in decision W 0040/07).

2. As far as the payment of fees is concerned, the applicant was invited with the communication of 13 August 2007 ("Form PCT/ISA/228 (April 2005)") to pay the protest fee within one month. In a letter dated 22 August 2007 the applicant requested the debiting of the protest fee from his deposit account. Thus, the payment was made in time, and the protest is considered to have been made (Rule 40.2(e) PCT, second sentence).

3. Moreover, the protest complies with the requirements of Rule 40.2(c) PCT and is therefore admissible.

4. The general requirements for protest proceedings are as follows:

4.1 Pursuant to Rule 40.2 PCT, the protest has to be examined and, to the extent that it is found to be justified, the full or partial reimbursement to the applicant of additional fees, as far as they were paid in fact and under protest, has to be ordered.

4.2 According to the established practice of the boards of appeal, the examination in protest proceedings has to be carried out in the light of the reasons given by the ISA in its invitation to pay additional fees under Rule 40.1 PCT and the applicant's submissions in support of the protest.

5. According to the PCT International Search and Preliminary Examination Guidelines (see Chapter 10, 10.66), the additional search fees must be paid for any protest to be considered. In the present case, additional search fees were paid for the groups of inventions 3 and 4. As a consequence, the board has to examine, whether the retaining of the two additional search fees is justified.

The appellant did not contest that the group of inventions 1 on the one side and the groups of inventions 3 and 4 on the other side did in fact belong to two different groups of inventions. The board has no reason to disagree. As a consequence, it remains to be evaluated whether there is unity between the groups of inventions 3 and 4.

6. The ISA's invitation to pay additional fees is based on the finding that there is lack of unity *a posteriori.* It was held that there was no single general inventive

concept in the light of the disclosure of several documents, including documents (4) and (6).

6.1 Document (4) discloses two series of phosphodiester ether lipid analogs with (N-methylmorpholino)ethyl or (N-methylpiperidino)ethyl polar head groups and long aliphatic or alkoxyethyl chains in the nonpolar portion of the molecule according to the formulae in figure 1 and their use as antineoplastic agents. The cytotoxic activity of these compounds (9-19) was evaluated *in vitro* (see table 1). Analog 17, which turned out to be the most potent compound of the series, has a N-methylpiperidinyl head group and a C16 alkyl chain (see page 2610, figure 1 and page 2611, last paragraph of the left-hand column). This compound corresponds to formula (I) of present claim 1, wherein R1 = R5 = C16H33, n = 0, W = X = Y = O, R6 = R7 = H, p = 2, and R8 = (i).

6.2 Document (6) discloses liposomes comprising a phospholipid as active agent for the treatment and/or prophylaxis of diseases caused by protozoons, tumors or bacteria (see page 19, line 20 - page 20, line 33). Example 1 discloses compositions comprising octadecyl-1-PC (PC = phosphatidylcholine), hexadecyl-PC, heptadecyl-PC or nonadecyl-PC as active agent (see page 25, lines 1 and 26-27). Octadecyl-PC corresponds to formula (I) of present claim 1, wherein R1 = R5 = C18H37, n = 0, W = X = Y = O, R6 = R7 = H, p = 2, and R8 = VR9R10R11, wherein V = N and R9 = R10 = R11 = CH3.

7. By arguing that there is no new technical effect linking the different groups of inventions and that the

compounds neither share a significant structural element nor belong to a same recognised class of chemical compounds, the ISA referred to the "Markush Practice" as described in paragraph (f) of Annex B of the Administrative Instructions under the PCT, which are binding as regards the assessment of unity for the ISA as well as for the board (see Article 2 of the Amended Agreement between the EPO and the International Bureau of WIPO, OJ EPO 2001, 601-609 and W 0003/94 (OJ EPO 1995, 775-783), point 10 of the reasons). Annex B, paragraph (f) specifies certain criteria for assessing unity of Markush claims, and in particular that for alternatives contained in such claims the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2 of the regulations under the PCT is considered to be met when the alternatives are of a similar nature. Alternatives are to be regarded as "of a similar nature" where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, and

(B)(1) a common structure is present, i.e. a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognised class of chemical compounds in the art to which the invention pertains.

A "recognised class of chemical compounds" under

(B)(2) above means that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved (Annex B, paragraph (f)(iii)).

7.1 As regards the groups of inventions 3 and 4, there exists a common property or activity in the form of the antimicrobial and antitumor activities of the compounds comprised therein, so that the requirements of point (A) above are met. Moreover, there are common structural elements as required in point (B)(1) above, which can be defined as follows: n = 0, R5 = C8-C30-alkyl and p = 1-6. In addition, the compounds comprise a quaternary nitrogen.

7.2 However, the fact that all claimed alternatives of the groups of inventions 3 and 4 belong to a group or a class of compounds which has a common structure and a common property or activity, can be regarded as a contribution over the prior art (see Rule 13.2 of the Regulations under the PCT) only if members of the group have not previously been used in the manner disclosed in the application under appeal. This is not the case in view of for instance documents (4) and (6) as was indicated above under points 6.1 and 6.2. As a consequence, these common structural and functional elements do not make a contribution over the prior art and can therefore not be considered as "special technical features". Therefore, there is lack of unity between the groups of inventions 3 and 4.

7.3 It is noted that in the invitation to pay additional fees, the groups of inventions 3-5 and 9-11 were characterized by p = 1-10, whereas in claim 1, p stands for 0-6. However, in view of the fact that in all the prior art compounds specifically mentioned in the invitation to pay additional fees, p is within the range of 1-6, it is immediately clear that the non-unity objections are valid for compounds wherein p = 1-6.

8. Further arguments of the applicant

8.1 The compounds of the alleged groups of inventions 3-4 are linked by a new technical effect, i.e. the anti-bacterial activity.

This argument cannot be successful in the light of the teaching of document (6), which mentions the antibacterial activity of the active agents disclosed therein.

8.2 The alkylphospholipid derivates shared the same or similar structural features to such an extent that the additional work was negligible, since mostly only the parameters "p" and "n" were varied, whereas the structural backbone remained essentially unchanged.

According to the PCT International Search and Preliminary Examination Guidelines Chapter 10, 10.65, the examiner, having found lack of unity, may in exceptional circumstances be able to establish both an international search and opinion covering more than one invention with negligible additional work and decide that the request for additional fees is not justified.

Nevertheless, it is fully within the examiner's discretion to decide on this matter. In the present case the ISA came to the conclusion that the total amount of additional work justified the request for the additional fees. In this context, it is noted that the board is not in a position to examine this decision, unless the discretion was not correctly applied. However, in the present case, the board cannot find any reason for an incorrect application of said discretion.

Order

For these reasons it is decided that:

The protest is dismissed.

The Registrar: The Chairman:

C. Eickhoff H. Kellner