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Datasheet for the decision of 5 October 2006

Case Number: T 0456/06 - 3.3.02

Application Number: 94106083.2

Publication Number: 0629409

IPC: A61K 49/00

Language of the proceedings: EN

Title of invention:
Tetrapyrrole carboxylic acid derivatives for diagnosis and/or therapy of arthritis

Applicant:
NIPPON PETROCHEMICALS CO., LTD.

Opponent:
-

Headword:
Diagnosis and therapy of arthritis/NIPPON PETROCHEMICALS

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no): concludent application of known use"

Decisions cited:
-

Catchword:
-

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Case Number: T 0456/06 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 5 October 2006

Appellant: NIPPON PETROCHEMICALS CO., LTD.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 16 January 2001 refusing European application No. 94106083.2 pursuant to Article 97(1) EPC.**

Composition of the Board:

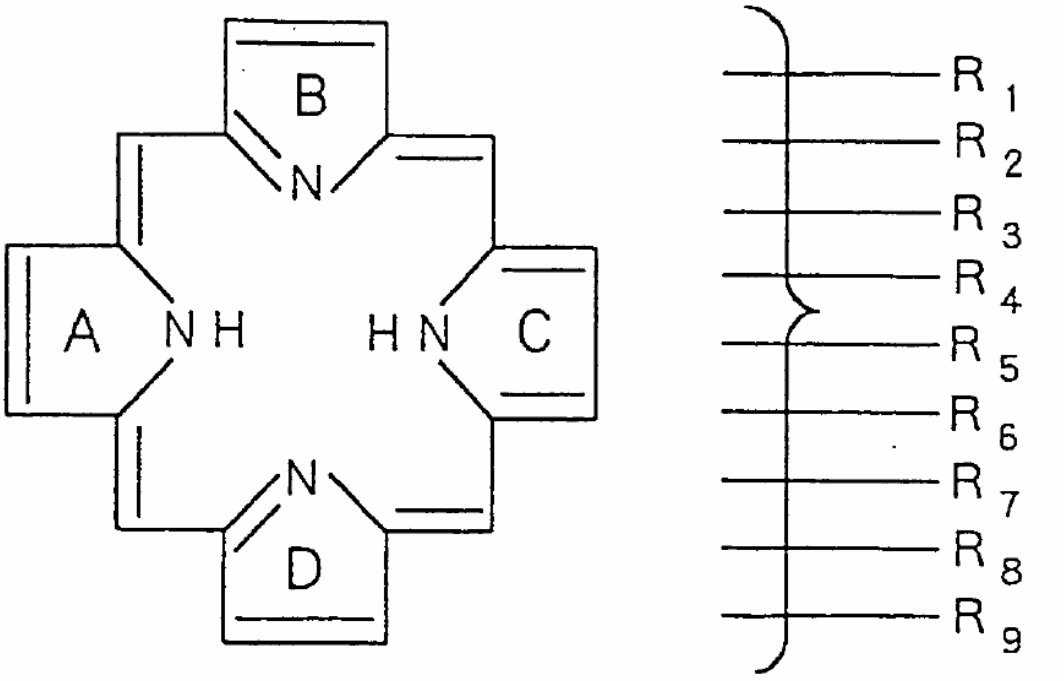
Chairman: U. Oswald
Members: H. Kellner
J. Willems

Summary of Facts and Submissions

I. European patent application No. 94 106 083.2 was refused by a decision of the examining division on the basis of Article 97(1) EPC for lack of novelty under Article 54 EPC.

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

"Use of at least one fluorescent compound for the preparation of a medical agent for diagnosis and/or therapy of arthritis of mammals; wherein said fluorescent compound is selected from the group consisting of tetrapyrrole carboxylic acids having at least one carboxyl group and the corresponding dihydrotetrapyrrole or tetrahydrotetrapyrrole carboxylic acids, and monoamides, diamides and polyamides of said tetrapyrrole carboxylic acids with amino-monocarboxylic acids or dicarboxylic acids, and their pharamacologically acceptable salts; wherein said tetrapyrrole carboxylic acid is represented by the following general formula:



wherein, R_1 is methyl, $\begin{bmatrix} -H \\ -CH_3 \end{bmatrix}$ or $\begin{bmatrix} -OH \\ -CH_3 \end{bmatrix}$;

R_2 is H, vinyl, ethyl, $-CH(OH)CH_3$, acetyl, $\begin{bmatrix} -H \\ -ethyl \end{bmatrix}$, $-\overset{\overset{O}{\|}}{C}-H$,

$-CH_2CH_2COOH$ or $=CHCHO$;

R_3 is methyl, $\begin{bmatrix} -H \\ -CH_3 \end{bmatrix}$ or $\begin{bmatrix} -CH_3 \\ -OH \end{bmatrix}$;

R_4 is H, vinyl, ethyl, $-CH(OH)CH_3$, $-CH_2CH_2COOH$, $=CHCHO$

or $\begin{bmatrix} -H \\ -ethyl \end{bmatrix}$;

R_5 is methyl;

R_6 is H, $-CH_2CH_2COOH$, $-CH_2CH_2COOR$ or $-COOH$;

R_7 is $-CH_2CH_2COOH$, $-CH_2CH_2COOR$ or $\begin{bmatrix} -CH_2CH_2COOH \\ -H \end{bmatrix}$;

R_8 is methyl or $\begin{cases} -CH_3; \\ -H \end{cases}$

R_9 is H, -COOH, $-CH_2COOH$ or methyl;

provided that when R_1, R_2, R_3, R_4, R_7 and R_8 represent two substituents or are divalent and attached to the same carbon, the respective pyrrole ring to which attached is a dihydropyrrole;

R is lower alkyl or benzyl;

R_6 and R_9, taken together are $-\overset{\displaystyle -C=O}{\underset{\displaystyle -CH_2}{|}}$ or $-\overset{\displaystyle -C=O}{\underset{\displaystyle -CHCO_2CH_3}{|}}$;

with the proviso that at least one of R_1 to R_9 is a free carboxyl group;

wherein the diagnosis comprises administering to a mammal an effective amount of said fluorescent compound that accumulates in an arthritic lesion and applying laser beams of sufficient wavelength and intensity to produce fluorescence in the joint cavity of said arthritic lesion; and the therapy comprises administering to a mammal an effective amount of said fluorescent compound that accumulates in an arthritic lesion and applying laser beams of sufficient wavelength and intensity to produce a cytotoxic effect in the joint cavity of said arthritic lesion."

II. The following documents were cited inter alia during the proceedings before the examining division and before the board of appeal:

(1) V.A. Tauraitis et al, "Evaluation of the possibility of using the photodynamic effect in

rheumatology", Biophysics (English translation of Biofizika), 1992, Vol. 37, No. 2, 269-274.

(4) EP-A-200 218

(5) WO-A-94/12 239 (Article 54(3) EPC)

III. The examining division considered that the subject-matter of claim 1 was not new with respect to document (5).

This document disclosed the use of one of the preferred compounds in the application, namely chlorin e_6 for the treatment of arthritis.

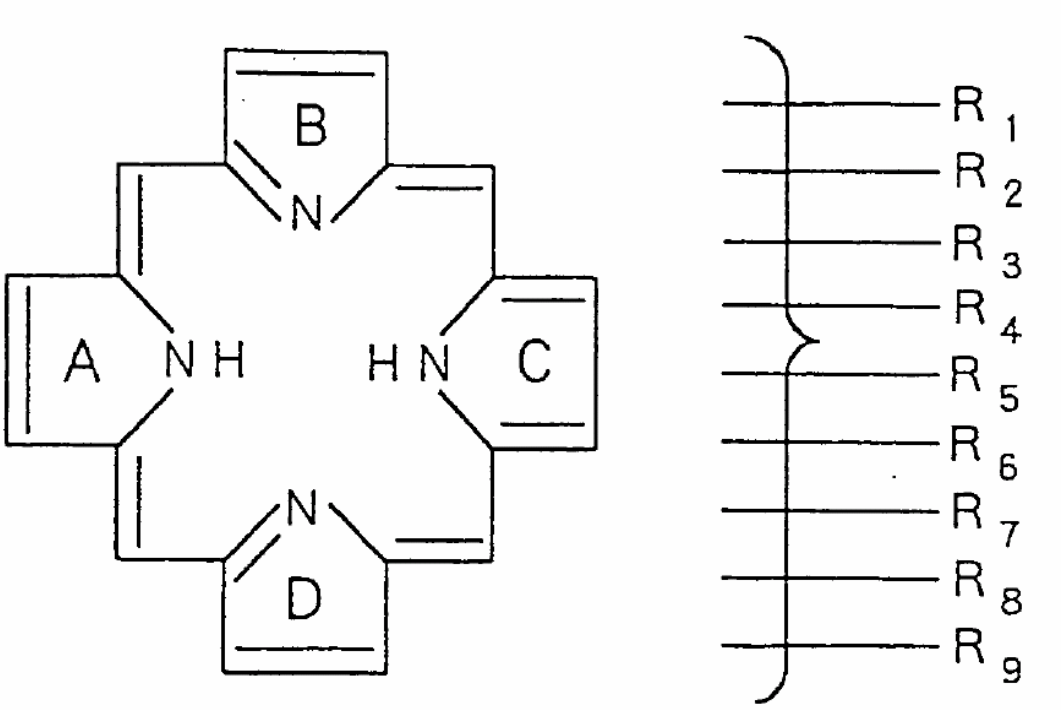
IV. The appellant lodged an appeal against the decision of the examining division.

With a letter of 22 August 2006 it filed two new sets of claims as main request and auxiliary request.

The wording of claim 1 of the main request is:

"Use of a fluorescent compound for the preparation of a medical agent for diagnosis of arthritis of mammals, wherein said fluorescent compound is selected from the group consisting of tetrapyrrole carboxylic acids having at least one carboxyl group and the corresponding dihydrotetrapyrrole or tetrahydrotetrapyrrole carboxylic acids, and monoamides, diamides and polyamides of said tetrapyrrole carboxylic acids with amino-monocarboxylic acids or dicarboxylic acids, and their pharamacologically acceptable salts;

wherein said tetrapyrrole carboxylic acid is represented by the following general formula:



wherein, R_1 is methyl, $\begin{bmatrix} -H \\ -CH_3 \end{bmatrix}$ or $\begin{bmatrix} -OH \\ -CH_3 \end{bmatrix}$;

R_2 is H, vinyl, ethyl, $-CH(OH)CH_3$, acetyl, $\begin{bmatrix} -H \\ -ethyl \end{bmatrix}$, $-\overset{\overset{O}{\|}}{C}-H$,

$-CH_2CH_2COOH$ or $=CHCHO$;

R_3 is methyl, $\begin{bmatrix} -H \\ -CH_3 \end{bmatrix}$ or $\begin{bmatrix} -CH_3; \\ -OH \end{bmatrix}$

R_4 is H, vinyl, ethyl, $-CH(OH)CH_3$, $-CH_2CH_2COOH$, $=CHCHO$

or $\begin{bmatrix} -H \ ; \\ -ethyl \end{bmatrix}$

R_5 is methyl;

R_6 is H, $-CH_2CH_2COOH$, $-CH_2CH_2COOR$ or $-COOH$;

R_7 is $-CH_2CH_2COOH$, $-CH_2CH_2COOR$ or $\begin{cases} -CH_2CH_2COOH; \\ -H \end{cases}$

R_8 is methyl or $\begin{cases} -CH_3; \\ -H \end{cases}$

R_9 is H, $-COOH$, $-CH_2COOH$ or methyl;

provided that when R_1, R_2, R_3, R_4, R_7 and R_8 represent two substituents or are divalent and attached to the same carbon, the respective pyrrole ring to which attached is a dihydropyrrole;

R is lower alkyl or benzyl;

R_6 and R_9, taken together are $-\underset{\underset{-CH_2}{|}}{C=O}$ or $-\underset{\underset{-CHCO_2CH_3}{|}}{C=O}$;

with the proviso that at least one of R_1 to R_9 is a free carboxyl group."

Claim 1 of the auxiliary request of 22 August 2006 reads (Differences with respect to the main request written in bold letters):

"Use of a fluorescent compound for the preparation of a medical agent for diagnosis of arthritis of mammals; **wherein the diagnosis comprises administering to a mammal an effective amount of said fluorescent compound that accumulates in an arthritic lesion and applying laser beams of sufficient wavelength and intensity to produce fluorescence in said arthritic lesion;** wherein said fluorescent compound is selected from the group consisting of tetrapyrrole carboxylic acids having at least one carboxyl group and the corresponding

dihydrotetrapyrrole or tetrahydrotetrapyrrole carboxylic acids, and monoamides, diamides and polyamides of said tetrapyrrole carboxylic acids with amino-monocarboxylic acids or dicarboxylic acids, and their pharamacologically acceptable salts; wherein said tetrapyrrole carboxylic acid is represented by the following general formula:

[see main request]"

V. Oral proceedings took place on 5 October 2006. At the oral proceedings, after discussion, the appellant sought to file two additional sets of claims as second and third auxiliary requests.

Claim 1 of the second auxiliary request reads (Differences with respect to the main request written in bold letters):

"Use of a fluorescent compound for the preparation of a medical agent for diagnosis of **the degree of arthritic inflammation** of mammals, wherein said fluorescent compound is selected from the group consisting of tetrapyrrole carboxylic acids having at least one carboxyl group and the corresponding dihydrotetrapyrrole or tetrahydrotetrapyrrole carboxylic acids, and monoamides, diamides and polyamides of said tetrapyrrole carboxylic acids with amino-monocarboxylic acids or dicarboxylic acids, and their pharamacologically acceptable salts; wherein said tetrapyrrole carboxylic acid is represented by the following general formula:

[see main request]"

The third auxiliary request was not admitted to the proceedings. With respect to the subject-matter of the main request, it was restricted to special groups of fluorescent compounds.

VI. The arguments of the appellant both in the written procedure and in the oral proceedings may be summarised as follows:

The subject-matter of the application in suit was new, since document (1) related only to the therapy of arthritis and not to its diagnosis, and since all other documents in the proceedings were even more distant.

Using document (1) as the closest state of the art, the skilled person would not regard document (4) to be pertinent because it related to cancer and not to arthritis. Even if he would take into account this document, he would find no incentive that diagnosis would work on arthritic lesions as well as on malignant cells of cancer. On the contrary, in document (1) the differences between cancer and arthritis were emphasised, making it inappropriate to deduct any teaching from the one disease to the other.

VII. The representative requested that the decision under appeal be set aside and that a patent be granted on the basis of one of the sets of claims of the main request or auxiliary request, filed on 22 August 2006, or of the second auxiliary request filed during the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. The amended claims filed by the appellant as main request and first and second auxiliary requests represent an attempt to overcome the objections raised during the proceedings. Consequently, they are admitted into the proceedings.

3. The set of claims which the appellant sought to introduce during the proceedings as third auxiliary request was late-filed and provided no answer to newly-raised arguments.

   Additionally, these claims were amended in a way that required a highly complex further assessment.

   The set of claims of the third auxiliary request was therefore not admitted into the proceedings.

4. The claims of the main request and the claims of the first and the second auxiliary requests may be seen as being based on the claims and the description as originally filed.

   The board is satisfied that the formal requirements of Articles 84, 83 and 123(2) EPC are formally fulfilled.

5. The subject-matter of the main request and the subject-matter of the first and the second auxiliary request is new with respect to documents (5) and (1). Neither these documents nor the others which were introduced into the proceedings refer to diagnosis of arthritis

using the tetrapyrrole carboxylic acids as disclosed in the application in suit for preparation of a diagnostic agent (Article 54(1) EPC).

6. *Inventive step*

6.1 The subject-matter of the main request concerns the "Use of a fluorescent compound for the preparation of a medical agent for diagnosis of arthritis of mammals, wherein said fluorescent compound is selected from the group consisting of certain tetrapyrrole carboxylic acids", in particular chlorin e_6 (see page 10, table 1, third compound from the bottom of the table in the description as filed).

6.2 Document (1) represents the closest state of the art.

According to its text, this document relates to the use of one of the preferred compounds in the application in suit, namely chlorin e_6 for the treatment of arthritis of mammals (see in particular page 269, summary and page 273, last paragraph).

6.3 In the absence of any comparative study with respect to document (1) as closest state of the art, the technical problem underlying the application in suit can only be seen in the provision of a further medical treatment, based on the use of chlorin e_6 or similar compounds for preparing the agent.

6.4 The solution to this problem is the provision of a medical agent exhibiting the features of claim 1 of the main request.

6.5 Having regard to the "example of diagnosis 1" and "test result 1" set out in the application in suit (see pages 45 to 47 with corresponding results on pages 48, line 13, to page 53, line 8, including tables 4 and 5 on pages 50 and 52 of the application as filed), the board is convinced that the problem has been solved.

6.6 However, in order to supply a further medical treatment, based on the use of chlorin e_6 for preparing the agent (see document (1)), the skilled person would take into account the teaching of document (4). Looking for any other use of said compound chlorin e_6, the person skilled in the art had to search for documents referring to it in the context of diseases.

European patent application (4) represents such a document. It refers to the use of specific tetrapyrrole carboxylic acids, namely such of the same kind as that referred to in document (1), in particular chlorin e_6, for therapy of cancer as well as for its diagnosis (see document (4), page 11, line 17, to page 15, line 36, with respect to therapy/diagnosis, and for instance page 7, table I, and page 16, lines 9 to 11, with respect to the mentioning of chlorin e_6).

With respect to the therapeutic or diagnostic use of chlorin e_6, it is clear from document (4) that therapeutic and diagnostic use are closely correlated (see in particular page 11, lines 17 to 27; page 12, lines 21 and 22; page 13, lines 21 and 22, and page 14, lines 15 to 17).

Once therapeutic use was established, whether for cancer or for arthritic lesions, it was totally clear

that all the medical possibilities referred to in document (4), being either therapy or diagnosis, were provided.

In trying to find a further medical treatment with respect to chlorin e_6 and arthritis, the person skilled in the art takes into account the teaching of (4) and accordingly is led to the use of chlorin e_6 for the diagnosis of arthritis.

6.7 Consequently, the board can only conclude that the subject-matter of claim 1 of the main request does not involve an inventive step.

6.8 The same holds for the subject-matter of the first auxiliary request, since the additional features of its claim 1 are mentioned in particular in (4) (see page 15, lines 30 to 32; page 12, lines 21 and 22; and page 14, lines 15 to 31), and thus the reasoning according to the subject-matter of the main request applies *mutatis mutandis*.

6.9 The subject-matter of claim 1 of the second auxiliary request differs from that of the main request in that a diagnosis of **the degree of arthritic inflammation** was to be achieved instead of diagnosis of arthritis in general.

The appellant refers to pages 52 and 53 of the application as filed, in particular lines 1 to 3 of page 52 and table 5. There, however, the measured "fluorescence intensity" is correlated with the "degree of swelling in mm of an inoculated right leg" and the "state of form and quantity of (hyperplastic) synovial

cells", meaning as finally decisive the number of affected cells. Therefore there is no difference in this additional feature of the second auxiliary request vis-à-vis the disclosure of document (4) because not only the existence and position but also the size of a tumour - meaning the size and number of tumour cells - can be determined (see (4), page 11, lines 17 to 27).

Thus, for the same reasons set out with respect to the main request and the auxiliary request dated 22 August 2006, the subject-matter of the second auxiliary request does not meet the provisions of Article 56 EPC.

7. With reference to the wording on page 269 in document (1) that the experience gained in oncology could not automatically be transferred to other disciplines and, in particular, to rheumatology, the appellant argued that the skilled person would never think that it would be possible to transfer this experience of oncology to diagnosis and therapy of arthritis and therefore would not take into account document (4).

Since, however, the outcome of the study published in document (1) showed that chlorin e_6 met the specific requirements to be used as a photosensitiser in rheumatology (see (1), enumeration on page 270, and page 273, last paragraph), this was the basis for the skilled person to use the photodynamic action of chlorin e_6 in rheumatology, while the photodynamic characteristics of chlorin e_6 contain therapy and diagnosis as well, as is set out in document (4).

Consequently, in these circumstances the arguments of the appellant cannot succeed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald