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**Datasheet for the decision
of 4 September 2009**

Case Number: T 0270/07 - 3.3.01

Application Number: 00962909.8

Publication Number: 1238977

IPC: C07D 401/04

Language of the proceedings: EN

Title of invention:

Process for the preparation of a pyridinemethanol compound

Patentee:

Sumitomo Chemical Company, Limited

Opponent:

Dr. Dominique J.M. Trösch
Krka, Tovarna Zdravil, d.d.

Headword:

Pyridinemethanol, Mirtazepine/SUMITOMO

Relevant legal provisions:

EPC Art. 56

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request: inventive step (yes) - improvements not obvious"

Decisions cited:

-

Catchword:

-



Case Number: T 0270/07 - 3.3.01

DECISION
of the Technical Board of Appeal 3.3.01
of 4 September 2009

Appellant I: Sumitomo Chemical Company, Limited
(Patent Proprietor) 5-33, Kitahama 4-chome
Chuo-ku
Osaka 541-8550 (JP)

Representative: HOFFMANN EITLE
Patent- und Rechtsanwälte
Arabellastrasse 4
D-81925 München (DE)

Appellant II: Dr. Dominique J.M. Trösch
(Opponent I) Ermlandstrasse 12
D-81929 München (DE)

Representative: Biagini, Giuditta
Breuer & Müller Partnerschaft
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Respondent: Krka, Tovarna Zdravil, d.d.
(Opponent II) Smarjeska cesta 6
SI-8501 Novo mesto (SI)

Representative: Gross, Ulrich-Maria; Nohlen, Martin
Uexküll & Stolberg
Patentanwälte
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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted
12 December 2006 concerning maintenance of
European patent No. 1238977 in amended form.

Composition of the Board:

Chairman: P. Ranguis
Members: G. Seufert
D. S. Rogers

Summary of Facts and Submissions

- I. Appellant I (Patent Proprietor) and Appellant II (Opponent I) lodged appeals against the interlocutory decision of the Opposition Division of 12 December 2006 maintaining the European patent no. 1 238 977 on the basis of the then pending first auxiliary request.
- II. In this decision the following numbering will be used to refer to the documents:
- (6) US 4 062 848
 - (7) J. March, "Advanced Organic Chemistry", fourth edition, 1992, John Wiley & Sons, New York (US), pages 1206-09,
 - (7a) J. March, "Advanced Organic Chemistry", fourth edition, 1992, John Wiley & Sons, New York (US), page 1212
 - (8) K. Peter C. Vollhardt, N. E. Schore, "Organische Chemie" second edition, 1995, VCH, Weinheim (DE), pages 838-839
 - (11) exhibit 1: Robert T. Morrison, Robert N. Boyd, Lehrbuch der Organischen Chemie, third edition, 1986, VCH Weinheim (DE), pages 901-902
- III. Notices of opposition were filed by Opponent I and Opponent II (Respondent) requesting revocation of the patent in its entirety on the grounds of lack of novelty and inventive step (Article 100(a) EPC in combination with Article 54 and 56 EPC).
- IV. The Opposition Division held that the subject-matter of the then pending first auxiliary request
- fulfilled the requirements of Article 123(2) EPC

and 84 EPC;

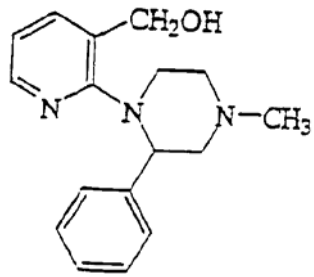
- was novel over the disclosure of document (6) due to the use of a different solvent
- involved an inventive step in view of the fact that the use of this solvent was not obvious in the light of document (6) or any of the other available prior art documents.

V. With the statement of grounds of appeal Appellant I filed a main request and first to third auxiliary requests, the first auxiliary request being the same as the request on the basis of which the Opposition Division maintained the patent in suit. In addition, Appellant I submitted exhibits no. 9 and 10 representing general knowledge in support of his arguments.

VI. In reply to the statement of grounds of appeal submitted by Appellant II, in particular in response to an objection under Article 84 EPC against claim 2 of the request as maintained by the Opposition Division referring to the process for the preparation of mirtazepine, Appellant I filed a new main request and new first to third auxiliary requests with its letter of 14 November 2007.

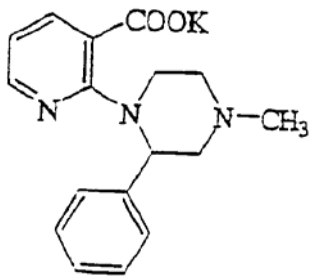
The main request consists of five claims, the independent claims 1 and 3 reading as follows:

1. A process for preparing a pyridinemethanol compound represented by the formula (II):



(II)

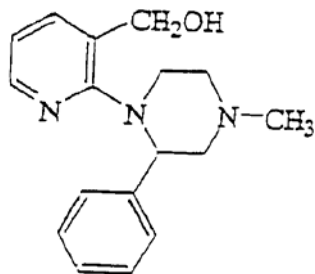
comprising reducing potassium pyridinecarboxylate represented by the formula (I):



(I)

with a metal hydride.

3. A process for preparing mirtazepine comprising the step of preparing a pyridinemethanol compound represented by formula (II):



(II)

in accordance with the process specified in Claim 1, followed by the step of adding said pyridinemethanol

- compound represented by the formula (II) to sulfuric acid.
- VII. With letter of 20 March 2008 Appellant I submitted an additional page of the same textbook as document (7), namely page 1212 (document (7a)).
- VIII. With the summons to oral proceedings, the Board sent a communication pursuant to Article 15(1) of the Rules of procedure of the Boards of Appeal (RPBA), indicating its preliminary opinion. In particular the Board raised concerns with respect to the admissibility of the amendments in claim 1 of auxiliary request 1 under Rule 80 EPC. Furthermore, the Board informed the parties that claim 3 of the main request appeared to be novel in view of the fact that the first reaction step was not disclosed in document (6). With regard to inventive step the Board considered it doubtful whether the arguments focussing on the yield and purity were pertinent in view of the fact that the provided calculations were valid for a two step process while claim 1 of the main request referred to only one step and in view of the fact that in example 2 of the patent in suit, which is also an example according to the invention, a product with the same melting point as in document (6) is obtained. An improvement might, however, be seen in the reduction of the amount of reducing agent as indicated in the patent in suit and the fact that apparently milder reaction conditions can be used.
- IX. In reply to the Board's communication Appellant I filed with letter of 4 August 2009 auxiliary requests 1a and 3a in an attempt to address the objection under Rule 80 EPC. Furthermore, he provided exhibits 1-3

representing the general knowledge of the skilled person to further support his arguments.

X. At the beginning of the oral proceedings before the Board, held on 4 September 2009, the Board inquired whether the Respondent, who contested the clarity and novelty of claim 3 of the main request before this request was replaced by the new main request of 14 November 2007, wished to maintain these objections in view of the fact that claim 3 of the new main request would appear to clearly include the reaction step of claim 1. The Respondent declared that he did not maintain these objections. Likewise Appellant II had no objections under Article 84 and 54 EPC against the main request.

XI. The arguments of Appellant I to the extent that they are relevant for this decision can be summarised as follows:

In view of document (6), which should be considered as the closest prior art, the problem to be solved by the patent in suit was the provision of a process capable of economically and efficiently preparing pyridinemethanol of formula (II) as already stated in the description of the disputed patent. This problem has been solved by reducing the potassium pyridinecarboxylate of formula (I), instead of the corresponding acid with a metal hydride, which allows the reduction to be carried out with less reducing agent and at milder reaction conditions. The proposed solution is not obvious from the combination of documents (6) and (7). Document (6) describes a variety of reaction routes to tetracyclic compounds and

realising where improvements may be made is already not obvious. Document (7) in table 19.3 might at first sight suggest the reduction of carboxylic acid salts; however, the reaction 9-38 (document (7a)) to which the table refers in this context contains no indication that it may be possible to reduce carboxylic acid salts with metal hydrides. Instead borane is suggested for this purpose. Even if the skilled person had considered table 19.3 on its own, it would not have provided him with information as to the reaction conditions required for the reduction of carboxylic acid salts. Being listed below the carboxylic acids and taking into account that according to table 19.3 the ease of reduction of functional groups decreases from top to bottom, the skilled person would expect the carboxylic acids salts to be more difficult to reduce than the carboxylic acids.

Furthermore, in view of the fact that according to the stoichiometry of the reaction the amount of reducing agent required in example (I) of document (6) would be 0.75 mole per mole pyridinecarboxylic acid and the fact that nevertheless 8 moles have been used per mole acid, the skilled person would realise that stoichiometric considerations are not decisive in the present case.

Although the reduction has been carried out in tetrahydrofuran (THF), which is a common solvent for the reducing agent lithium aluminium hydride (LAH), no evidence has been provided that other equally common solvents, like dimethylether, would not work equally well.

Furthermore, document (7) provides only a very general indication as to the suitability of other metal hydrides for the reduction of carboxylic acid and salts, which according to that document will be affected by the nature of the chemical structure to which the carboxylate group is attached. It therefore does not represent proper evidence that the reduction of the presently claimed specific pyridinecarboxylate with other metal hydride, like those mentioned in paragraph [0042] of the patent in suit, will fail.

- XII. The arguments of the Respondent to the extent that they are relevant for this decision can be summarised as follows:

The subject-matter of the patent in suit is obvious in view of example I of document (6) in combination with common general knowledge as illustrated by document (7), in particular in view of table 19.3 of document (7) referring to the reduction of carboxylic acid salts with LAH. The advantage of using less reducing agent would be obvious for the skilled person in view of his general knowledge reflected in document (8) that the first step in the reduction of carboxylic acids with LAH is the formation of the corresponding salts which consumes part of the reducing agent. If the salt is used as starting material this first step would no longer be necessary and the amount of LAH could be reduced. Furthermore, taking into account that less reducing agent would be required when starting from the carboxylic acid salt, the patent in suit in view of the stoichiometry of the reaction as illustrated in document (8) works with the same 10 fold excess of reducing agent as example I in document (6).

The milder reaction conditions require extensive cooling as the reduction is highly exothermic, which is the reason for the high reaction temperature in example (I) of document (6). Such a cooling cannot be considered advantageous.

Furthermore, the alleged advantages are only associated with specific measures which are not reflected in the claim. In particular it is essential that tetrahydrofuran is used, in which the hydride is dissolved.

In view of table 19.5 of document (7), which indicates that not all metal hydrides might be suitable to reduce carboxylic acid salts, it is also not apparent from the patent in suit that the underlying technical problem has been solved over the whole scope of the claims.

- XIII. Appellant II agreed with the arguments put forward by the Respondent and did not submit additional arguments relevant for this decision.

- XIV. Appellant I requested that the decision under appeal be set aside, that the appeal of Appellant II be dismissed and that the patent be maintained on the basis of the main request filed with letter of 14 November 2007, or one of the first to third auxiliary requests filed on the same date, or one of the auxiliary requests 1a and 3a filed with letter of 4 August 2009.

The Appellant II requested that the decision under appeal be set aside, that the patent be revoked and that the appeal of Appellant I be dismissed.

The Respondent requested that the appeal of Appellant I be dismissed.

- XV. At the end of the oral proceedings, the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. *Amendments (Article 123(2) and (3) EPC)*

The amendment made to claim 3 as granted, namely the addition of the step of preparing a pyridinemethanol compound represented by formula (II) in accordance with the process specified in claim 1, is properly supported by the application as originally filed (see page 1, lines 7-11 of the description as filed and original claims 1 and 3). The addition of a second reaction step further restricts the scope of this claim. The amendment, therefore, complies with the requirements of Article 123(2) and (3) EPC.

3. *Clarity and novelty*

Clarity of claim 3 of the main request and its novelty over the disclosure of document (6) was no longer under dispute (see point X above). The Board, in view of the fact that claim 3 clearly refers to a two step process, a point of dispute before the main request was amended,

and the fact that document (6) does not disclose the first step of this process, sees no reason to take a different view.

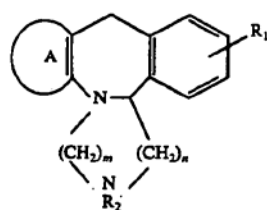
Hence, the subject-matter of the main request meets the requirement of Article 84 EPC and is novel in the sense of Article 54 EPC.

4. *Inventive step*

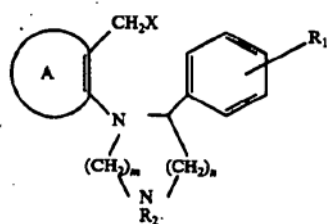
4.1 It is established jurisprudence of the Boards of Appeal, that in order to assess inventive step it is necessary to establish the closest state of the art, to determine in the light thereof the technical problem which the invention addresses and successfully solves and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

The patent in suit is directed to the reduction of the potassium pyridinecarboxylate of formula (I) with a metal hydride to obtain the pyridinemethanol compound of formula (II) and, furthermore, to the preparation of mirtazepine comprising said reduction step followed by a cyclisation step with sulfuric acid.

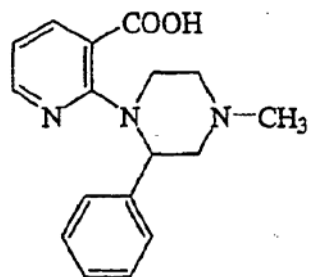
4.2 A similar reaction sequence for the preparation of mirtazepine is known from document (6). This document describes the preparation of tetracyclic compounds of formula (I) including mirtazepine:



Various possibilities of preparing the compounds of formula (I) are described, among them the condensation of compounds according to formula (II) whereby X is hydroxyl, etherified or esterified hydroxyl, or halogen.



Compounds of formula (II) can be prepared in a variety of ways; one of the possibilities is shown in the flow sheet in columns 3 and 4 of document (6). Example I of document (6) describes the preparation of mirtazepine using the corresponding compound of formula (II) (i.e. m and $n = 2$, $R_2 = \text{methyl}$, R_1 is hydrogen and $A =$ pyridine ring with the nitrogen atom adjacent to the carbon bearing the nitrogen of the piperidine ring), which has been prepared by reducing the acid form (IV) with LAH:



(IV)

4.3 Document (6) is cited in the patent in suit which further indicates several disadvantages in the individual process steps set out in document (6). In particular, it was pointed out that in document (6) a large excess of LAH, namely 8 times equivalent based on the pyridinecarboxylic acid, was used in the reduction step of compound (IV) to compound (II). In view of this prior art it was an object of the invention, as indicated on page 2, lines 57-58 of the patent in suit and as confirmed by the Appellant I at the oral proceedings before the Board, to provide a process capable of economically and efficiently preparing the pyridinemethanol compound of formula (II).

As the solution to this underlying technical problem the patent in suit proposes the use of potassium pyridinecarboxylate as starting material in the reduction process.

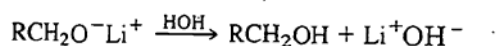
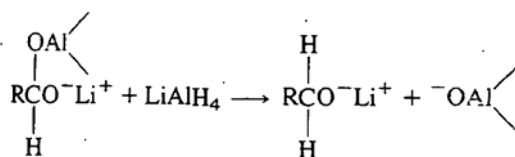
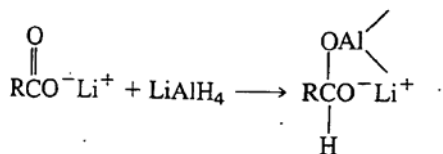
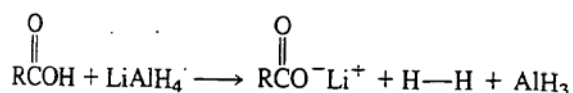
4.4 The Board notes that the reduction according to the examples of the patent in suit using the same reducing agent in the same solvent and the same sequence of addition of the reagents as example I in document (6), on a laboratory scale (as in example I of D6) as well as on a semi-industrial scale, requires only about half the amount of reducing agent, or even less, compared to the amount used in the prior art (see examples 2 and 4

of the patent in suit). In addition, the reduction according to the patent in suit is carried out at a temperature between 20°C and 30°C, conditions which are much milder compared to the conditions of document (6) (i.e. boiling temperature throughout the reaction). It is to be remarked that in order to establish the existence of these improvements that relate purely to the reduction step, it is not pertinent whether there are differences in the work-up procedure that takes place after the reduction step or whether the yield over the two-step reaction sequence of dependent claim 2 of the disputed patent has been improved or not. These issues were extensively discussed during the opposition procedure as well as in the Appellants' statement of grounds of appeal and the respondent's reply.

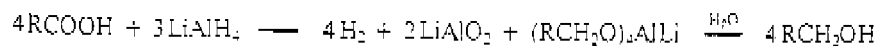
4.5 The decrease of the amount of reducing agent as well as the reduction of the reaction temperature from boiling point to between 20° and 30°C represent, in the opinion of the Board, in particular on an industrial or semi-industrial scale, considerable advantages. The Board is thus satisfied that the problem as defined in the patent in suit (point 4.3 above) has been solved. Hence, the issue whether or not there are additional advantages regarding the purity of the obtained crystals or an improvement in yield and who has the burden of proof for demonstrating these advantages does not need to be decided.

4.6 It remains to be decided whether or not the proposed solution is obvious in view of the prior art.

4.7 The Respondent argued that the solution to this problem would be obvious in view of document (6) and the general knowledge of the skilled person illustrated by document (7). According to table 19.3 of document (7) carboxylic acids as well as carboxylic acid salt can be reduced with LAH as reducing agent. The reduction in the amount of LAH would have been expected by the skilled person in view of document (8) and document (11), both reflecting general knowledge. Document (8) describes the presumed reaction mechanism of the reduction of carboxylic acid with LAH consisting of four steps: salt formation, hydride addition, substitution by hydride and hydrolysis:



Since the first step, namely the salt formation, would no longer be necessary if, as claimed, a salt is used as starting material, it would be obvious to the skilled person that the amount of LAH could be reduced. Furthermore, document (11) describes on page 901 the stoichiometry of the reaction, namely



Taking into account that according to this equation 0.75 mol LAH are required for the reduction of 1 mol acid (i.e. $4/3 = 1/0.75$), document (6) works with a 10 fold excess of LAH (8 moles LAH per 1 mol acid). With one mol less required due to the use of the carboxylic acid salt (see first step of document (8)) the equation on the left side would be $4\text{RCOO}^- + 2\text{LiAlH}_4$. Thus, the required moles of LAH would be $4/2 = 1/0.5$. With a preferred value of 5 moles LAH per mole potassium salt according to page 6, line 41 of the patent in suit, the excess used in the process according to the disputed patent is actually the same as in document (6), i.e. ten fold.

- 4.8 Considering the milder reaction conditions the Respondent submitted that in his opinion the reaction is exothermic, which is the cause for the high reaction temperature in example (I) of document (6). To keep the reaction between 20°C and 30°C would require cooling and therefore would not represent an advantage.

Appellant II did not submit additional comments.

- 4.9 The Board is not convinced by the above arguments of the Respondent.
- 4.9.1 As mentioned in point 4.2 above, document (6) refers in general to the preparation of tetracyclic compounds of formula (I), including mirtazepine, using alcohol derivatives of formula (II). The compounds of formula (II) can be prepared in a variety of ways and the reduction of the carboxylic acid compound with LAH as

mentioned in column 3 and 4 and illustrated in example I is part of one of the possible routes. There are also other routes indicated which could be used to obtain mirtazepine without the need of a compound of formula (II) and, consequently, a reduction step. Furthermore, the skilled person also has methods other than the reduction of a carboxylic acid at his disposition for the introduction of a $-CH_2OH$ group. There is no suggestion in document (6) as to the use of a carboxylic acid salt in the reduction step. Therefore, document (6) does not by itself render the claimed subject-matter obvious.

4.9.2 Document (7) describes in table 19.3 the reduction of various functional groups among them carboxylic acids and salts with LAH. In table 19.3 reference is made to the reaction 9-38 on page 1212 of the same textbook (document (7a)). The reaction 9-38 is entitled "Reduction of Carboxylic Acids to Alcohols" and refers to the use of LAH as well as other hydrides as suitable reducing agents for carboxylic acids. Borane is mentioned as particularly good for carboxylic acids permitting selective reduction in the presence of many other groups. The only reference in reaction 9-38 to carboxylic acid salts is in combination with borane as a reducing agent. Furthermore, document (7) is entirely silent on the reaction conditions required to reduce carboxylic acid salts. There is also no information in any of the other pieces of the prior art which would demonstrate that it is part of the general knowledge of the skilled person that carboxylic acid salts would be easier to reduce than the corresponding acids. In fact there is no prior art document available explicitly

showing the reduction of carboxylic acid salts and suitable reaction conditions.

- 4.9.3 Thus, the skilled person when trying to solve the technical problem underlying the patent in suit, i.e. the provision of a more economic and efficient process for the preparation of compound (II), would have found no motive in document (7) to use the potassium carboxylate as starting material for the reduction reaction.
- 4.10 With respect to the calculations made by the Respondent the Board notes that these calculations can be easily made knowing the invention, i.e. in hindsight. However, even if the skilled person could have made these calculations in advance, there would only be a punctual overlap (at 5 moles reducing agent), which loses importance when considering the mentioned range in the patent in suit, i.e. 2.5 to 5 moles reducing agent per mole potassium carboxylic, and especially the preferred area, i.e. 3 to 4 moles reducing agent, which is reflected in the examples of the patent in suit. Thus, taking into account the aforementioned calculations less than a 10 fold excess of reducing agent is necessary in the claimed reduction process. In addition, these calculations do not explain the mild reaction conditions that can be used.
- 4.11 In the opinion of the Board, the Respondent's explanation with respect to the milder reaction conditions are not convincing. The Respondent has not provided any data and/or calculation, which could plausibly support his allegation that the reduction reaction is so highly exothermic that it keeps the

reaction mixture at boiling point for the whole duration of the four hours as required in example I of document (6), or that extensive cooling would be required in the process according to the patent in suit. Furthermore, the prior art example describes the addition of the carboxylic acid to a boiling suspension of LAH in THF which clearly requires that the reflux conditions are already provided before the reaction starts. Without any data or corroborating evidence the Respondent's arguments are mere speculation.

4.12 The Respondent further submitted that the alleged advantages have not been supported over the whole scope of the claims. In this context the Respondent referred to table 19.5 of document (7), where several metal hydrides are listed, which allegedly would not reduce carboxylic acid salts. In particular, the Respondent pointed to $(i\text{-Bu})_2\text{AlH}$ (DIBAL), which was mentioned as one of the reducing agents in the patent in suit and which according to table 19.5 would not be suitable to reduce carboxylic salts. Furthermore, according to the respondent the alleged advantages are only associated with specific measures, like the use of THF, which dissolves the reducing agent.

4.13 The Board, however, observes that table 19.5 in document (7) merely gives a general indication on the reactivity of various functional groups with some metal hydride. In the opinion of the Board, some of the apparently non-working reducing agents are not even metal hydrides, for example $\text{BH}_3\text{-THF}$ or bis-3-methyl-2-butyl-borane. Table 19.5 does not contain specific details concerning the chemical structures of the acids or salts to be reduced, i.e. the nature of the variable

R. It is not even apparent whether in the column where DIBAL is mentioned as a reducing agent for a carboxylic acid but not for a carboxylic acid salt, the residue R is the same. Moreover, document (7) even acknowledges that the tables cannot be exact, because the nature of R and the reaction conditions can affect the reactivity (document (7), page 1206, last three lines before table 19.2). The Board furthermore observes that in table 19.5 borane has been characterised as not being able to reduce carboxylic acid salts, while in reaction 9-38 to which that table refers, borane has been identified as a suitable reducing agent, which raises some doubts as to the correctness of the data in table 19.5. With regard to the suggestion that the advantage of milder reaction conditions is only present when THF is used as the solvent the Board notes that the Respondent has not provided evidence for his allegation. Tetrahydrofuran is a preferred solvent for the reduction of LAH, but apparently also other solvents are suitable, like dimethylether (table 19.3 of document (6)).

Therefore, the submissions as put forward by the Respondent, who has the burden of proof for the facts that it alleges, cannot be accepted by the Board because it has not been convincingly shown that the specific potassium salt of the patent in suit cannot also advantageously be reduced by other metal hydrides, like the ones specified in the description, or in other solvents.

- 4.14 Thus, the Board concludes that the subject-matter of claim 1 of the main request filed with a letter of 14 November 2007 is not obvious to the skilled person

in the light of the cited documents and consequently involves an inventive step in the sense of Article 56 EPC.

- 4.15 In view of this outcome there is no need to consider the further auxiliary requests of Appellant I.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The appeal of Appellant II is dismissed.
3. The case is remitted to the department of first instance with the order to maintain the patent as amended in the following version:

Description:

Amended pages 2-11 of the patent specification received during oral proceedings of 4 September 2009

Claims:

No. 1-5 of the main request filed with letter of 14 November 2007

The Registrar:

The Chairman:

B. Atienza Vivancos

P. Ranguis