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File Number: T 383/88 - 3.3.1  
Application No.: 83 307 993.2  
Publication No.: 0 123 750  
Title of invention: Condensed amino pyrimidinones and their use in the  
treatment and prophylaxis of viral infections

Classification: C07D 239/70

D E C I S I O N  
of 1 December 1992

Applicant: Biomeasure Inc.

Headword: Pyrimidinones/BIOMEASURE

EPC Articles 54(1), (2), 123(2), 111(1)

Keyword: "Novelty - overlapping group of compounds"; "Extension beyond the content of the application as filed read in the light of common general knowledge - balance of probability is the wrong standard for deciding the allowability of amendments under Article 123(2) EPC - the slightest doubt as to the derivability of the amendment from the unamended document rules out the amendment - affidavit evidence"; "Remittal to the Examining Division"



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Boards of Appeal

Chambres de recours

Case Number : T 383/88 - 3.3.1

DECISION  
of the Technical Board of Appeal 3.3.1  
of 1 December 1992

Appellant : Biomeasure Inc.  
11-15 E. Avenue  
Hopkinton  
Massachusetts (US)

Representative : Deans, Michael John Percy  
Lloyd Wise, Tregear & Co.  
Norman House  
105-109 The Strand  
London WC2R 0AE (GB)

Decision under appeal : Decision of the Examining Division of the  
European Patent Office dated 1 February 1988  
refusing European patent application  
No. 83 307 993.2 pursuant to Article 97(1) EPC.

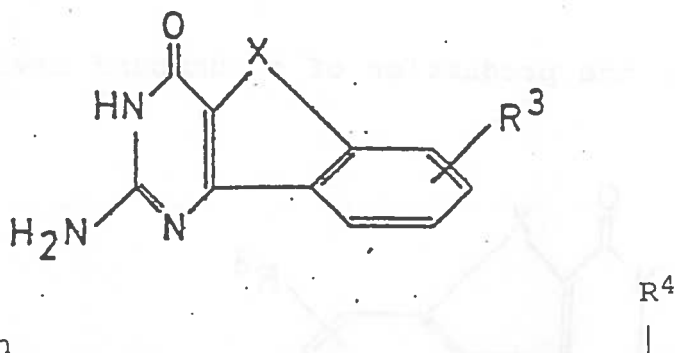
Composition of the Board :

Chairman : K.J.A. Jahn  
Members : J.M. Jonk  
J.A. Stephens-Ofner

Summary of Facts and Submissions

I. European patent application No. 83 307 993.2, filed on 29 December 1983 (publication No. 0 123 750), was refused by a decision of the Examining Division dated 1 February 1988. The decision was based on 10 claims for the Contracting States other than Austria, Claims 1 and 3 (filed on 2 July 1987) reading as follows:

"1. A compound having the formula:



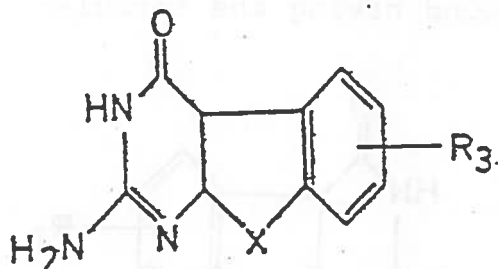
wherein

X is (CH<sub>2</sub>)<sub>n</sub> where 1 ≤ n ≤ 3; CH<sub>2</sub>-CH where R<sup>4</sup> is lower alkyl; CH<sub>2</sub>S; or CH<sub>2</sub>O; and

R<sup>3</sup> is H, lower alkyl; lower alkoxy, a halogen, C = N, nitro, amino, alkylamino, dialkylamino, arylamino, carboxy, or lower alkoxy-carbonyl; provided that, when n = 2, R<sup>3</sup> cannot be H or methoxy;

or a pharmaceutically acceptable salt thereof.

3. A compound having the formula



R<sup>4</sup>  
|

wherein

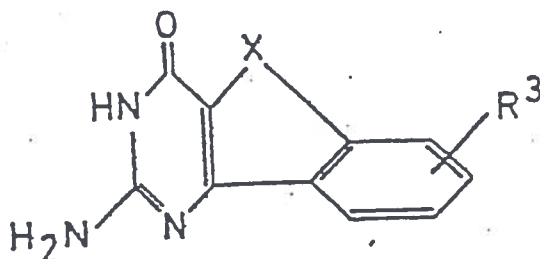
X is (CH<sub>2</sub>)<sub>n</sub> where 1 ≤ n ≤ 3; CH<sub>2</sub>-CH where R<sup>4</sup> is lower alkyl; CH<sub>2</sub>S; or CH<sub>2</sub>O; and

R<sup>3</sup> is H, lower alkyl, lower alkoxy, halogen, C = N, nitro, amino, alkylamino, dialkylamino, arylamino, carboxy, lower alkoxy-carbonyl;

or a pharmaceutically acceptable salt thereof."

and on nine claims for Austria, Claim 1 (filed on 2 July 1987) reading as follows:

"A method for the production of a compound having the formula:



R<sup>4</sup>  
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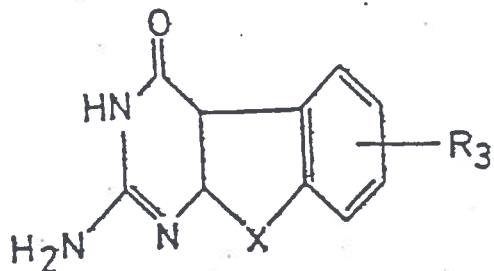
wherein

X is (CH<sub>2</sub>)<sub>n</sub> where 1 ≤ n ≤ 3; CH<sub>2</sub>-CH where R<sup>4</sup> is lower alkyl; CH<sub>2</sub>S; or CH<sub>2</sub>O; and

R<sup>3</sup> is H, lower alkyl; lower alkoxy, a halogen, C = N, nitro, amino, alkylamino, dialkylamino, arylamino, carboxy, or lower alkoxy-carbonyl; provided that, when n = 2, R<sup>3</sup> cannot be H or methoxy;

or a pharmaceutically acceptable salt thereof;

or a compound having the formula:



wherein

R<sup>4</sup>

X is (CH<sub>2</sub>)<sub>n</sub> where 1 ≤ n ≤ 3; CH<sub>2</sub>-CH where R<sup>4</sup> is lower alkyl; CH<sub>2</sub>S; or CH<sub>2</sub>O; and

R<sup>3</sup> is H, lower alkyl, lower alkoxy, halogen, C = N, nitro, amino, alkylamino, dialkylamino, arylamino, carboxy, lower alkoxy-carbonyl;

or a pharmaceutically acceptable salt thereof;

the method comprising the steps of providing the corresponding alpha-ketoester, reacting the same with guanidine, and retrieving the product."

- II. The stated grounds for the refusal were extension beyond the content of the application as filed with respect to the subject-matter of Claim 1 for Austria (Article 123(2) EPC), and lack of clarity of the subject-matter of Claims 1 and 3 for the Contracting States other than Austria and Claims 1, 4, 8 and 9 for Austria and lack of concision of Claim 4 for Austria (Article 84 EPC).

Regarding the subject-matter of Claim 1 for Austria the Examining Division held that it extended beyond the content of the application as filed because the originally filed application did not give any hint that conditions other than those indicated on page 5, lines 11 to 15, could be used in the preparation of the compounds concerned.

In Claims 1 and 3 for the Contracting States other than Austria and in Claims 1, 4, 8 and 9 for Austria, the radicals alkyl and alkoxy were limited by the term "lower". In the absence of any definition of this relative term, the Examining Division considered the subject-matter of the respective claims unclear, contrary to the provisions of Article 84 EPC.

With respect to Claim 4 for Austria, the Examining Division held that by referring therein to the definitions of the compounds in Claim 1, undue repetition of wording could be avoided.

- III. A notice of appeal was filed against this decision on 14 April 1988 and the appeal fee was paid on the same date.

A Statement of Grounds of Appeal, including a set of claims for the Contracting States other than Austria (Annex A), a set of claims for Austria (Annex B), and six alternative wordings for the final four lines of Austrian Claim 1 as auxiliary requests (Annex C), was filed on 10 June 1988.

- IV. In Claim 1 for Austria as indicated above, it was specified that the desired compounds could be prepared by reacting the corresponding  $\alpha$ -ketoester with a guanidine salt in an inert solvent.

Moreover, in Claims 1 and 3 for the Contracting States other than Austria and in Claims 1, 4, 8 and 9 for Austria the definition of the "lower" radicals was made more precise by indicating their maximum amount of carbon atoms, and in Claim 4 for Austria the undue repetition of wording was avoided.

- V. The Appellant argued that the skilled person, on reading the specification of the patent in suit in the light of common general knowledge at the relevant time, would immediately understand that the preparation of the desired compounds essentially comprised the reaction of a ketoester with a guanidine salt in an inert solvent as defined in present Claim 1 for Austria, so that the provisions of Article 123(2) EPC would be met.

VI. In a communication dated 12 December 1991, the Rapporteur indicated that, in the Board's preliminary view, the subject-matter of Claim 1 for the Contracting States other than Austria did not appear to be novel in the light of the disclosure of

(1) US-A-3 257 400.

Moreover, he noted that Claim 1 for Austria could only be accepted if it could be shown by means of standard textbooks that the use of guanidine salts other than a carbonate, and inert solvents other than xylene, were both clearly part of the common general knowledge at the relevant time.

VII. In a response to this communication filed on 13 May 1992 the Appellant restricted Claim 1 for the Contracting States other than Austria by disclaiming the overlapping group of compounds disclosed in document (1). Moreover, he filed an Affidavit to support the suggested amendment to Claim 1 for Austria.

VIII. In a further communication dated 24 August 1992, the Rapporteur indicated that in the Board's provisional view this Affidavit was of insufficient weight, and further drew attention to the Board's earlier request for evidence in the form of textbooks or the like.

IX. On 23 October 1992, the Appellant filed the following extracts from standard chemistry textbooks:

(2) "The Organic Chemistry of Drug Synthesis" by D. Ledmiller & L.A. Mitscher, 1977, pages 262 and 263, and Ref. 19: J. Am. Chem. Soc., 73 (1951), 3763 to 3770,

- (3) "Principles of Modern Heterocyclic Chemistry" by L.A. Paquette (1974), page 313,
- (4) "Contemporary Heterocyclic Chemistry" by G.R. Newkome & W.W. Pandler (1982), page 188, and
- (5) "An Introduction to the Chemistry and Biochemistry of Pyrimidines, Purines and Pteridines" by D.T. Hurst, (1980), pages 19 to 25 and 61,

in an attempt to demonstrate that the condensation reactions according to Claim 1 for Austria were well known. He also requested oral proceedings if Claim 1 were held to be unallowable.

- X. During oral proceedings, held on 1 December 1992, the Appellant replaced these claims by Claims 1 to 11 for the Contracting States other than Austria (Annex A), and Claims 1 to 12 for Austria (Annex B) (main request), and alternative Claims 1 to 12 for Austria (Annex C) (auxiliary request).

Claim 1 of the set of claims for the Contracting States other than Austria (Annex A) corresponded to Claim 1 indicated under section I above, except that the term "methoxy" in the disclaimer was replaced by "an alkoxy group with fewer than 6 carbon atoms at position 8". Additional Claim 11 of this set of claims was directed to the use of the now disclaimed compounds for the manufacture of a medicament for the treatment or prophylaxis of viral infections.

Claim 1 of the set of claims for Austria (Annex B) according to the main request corresponded to Claim 1 for Austria indicated under section I above, except that now the same compounds were disclaimed as in new Claim 1 for the other Contracting States and the term "guanidine" (last line) was replaced by "a guanidine salt in an inert



solvent". Additional Claims 10 to 12 of this set of claims related to methods for the production of therapeutic compositions or towlettes.

Moreover, in both sets of claims, particularly in Claims 1 and 3 of Annex A and Claims 1, 4, 8 and 9 of Annex B, the term "lower" was avoided by precisising the definition of the radicals alkyl and alkoxy in that they contained less than 6 carbon atoms.

In addition, in Claim 4 of Annex B, the undue repetition of wording was avoided.

The alternative set of claims for Austria according to the auxiliary request corresponded to that of the main request, except that in Claim 1 the starting compound "guanidine salt" was restricted to "guanidine carbonate".

The Appellant argued that the teaching in documents (2) to (5) clearly showed that the desired pyrimidine compounds could be prepared by reacting an appropriate  $\alpha$ -ketoester with a guanidine salt in the presence of an inert solvent. However, he admitted that none of the cited documents specifically related to the reaction of a ketoester with a guanidine salt other than guanidine carbonate.

- XI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims set out in Annexes A and B, both submitted in the course of oral proceedings (main request), or on the basis of the claims set out in Annexes A and C, also submitted during oral proceedings (auxiliary request).

XII. At the conclusion of the oral proceedings, the Board's decision to remit the case to the Examining Division for further prosecution on the basis of the claims set out in Annexes A and C according to the auxiliary request was announced.

#### Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC, and is therefore admissible.
2. Main request
  - 2.1 Clearness and concision of the claims under Article 84 EPC.
    - 2.1.1 In the present claims the relative term "lower" is avoided and replaced by a clear definition of the number of carbon atoms in the radicals concerned. Also the undue repetition of wording in Claim 4 for Austria is avoided. Therefore, the objections of the Opposition Division with respect to lack of clarity and lack of concision are met. Under these circumstances the Board sees no need for further consideration.
  - 2.2 Extension beyond the content of the application as filed under Article 123(2) EPC.
    - 2.2.1 According to the description of the patent application as filed (cf. page 5, lines 11 to 15), in order to prepare the desired compounds, a mixture of an appropriate  $\alpha$ -ketoester and guanidine carbonate in xylene is refluxed overnight, and the final product is then collected by filtration and purified. In addition, all the preparative examples use the same preparation conditions.

Therefore, the question to be considered is whether the generalisation of these preparation conditions to those set out in present Claim 1 for Austria, namely, to the steps of reacting the corresponding alpha-ketoester with a guanidine salt in an inert solvent, and retrieving the product, would amend the present patent application in such a way that it contains subject-matter which extends beyond the content of the patent application as filed.

- 2.2.2 Initially the Board would observe that according to the established jurisprudence of the Boards of Appeal to determine whether an amendment does or does not extend beyond the subject-matter of the application as filed, it is necessary to examine if the overall change in the content of the application originating from this amendment results in the skilled person being presented with information which is not directly and unambiguously derivable from that previously presented by the application, even when account is taken of matter which is implicit to a person skilled in the art in what has been expressly mentioned.

In decision T 113/86 this Board considered that amendments requested by the Patentee should not be allowed if there was the slightest doubt that the unamended patent could be construed differently to the patent as amended (cf. paragraph 2.2 of the Reasons).

This clearly means that the normal standard of proof in civil proceedings such as appeals before the Boards of Appeal, namely "the balance of probability", is inappropriate. Instead, a rigorous standard, i.e. one equivalent to "beyond reasonable doubt" is considered by the Board as being the right one to apply in such a case, for applying a lower standard could easily lead to undetected abuse by allowing amendments on the basis of ostensibly proven common general knowledge.

Now it is frequently argued that certain technical features can be directly and unambiguously derived from a specification as filed by reading it in the light of common general knowledge. However, this approach should be viewed with considerable caution, for common general knowledge is notoriously difficult to prove, even when all the various types of evidence permitted under Article 117 EPC are taken into consideration (cf. G 11/91, to be published in OJ EPO, headnote published in OJ EPO, 1-2/1993, III, section 8 of the Reasons). The difficulty lies mostly in gauging the degree of commonality, for whilst information may be generally disseminated, and therefore known within the community of skilled addressees, it may well, at the same time, not be commonly accepted. In other words, there may be differing views on the truth or falsity of the information and no less so if these views are expressed in standard textbooks. Nor can too much reliance be placed on affidavit evidence from over-qualified persons, for the relevant knowledge is that of the notional, i.e. average skilled addressee, and not that commanded by leaders in the relevant scientific discipline or field.

- 2.2.3 In the present case, the evidence adduced by the Appellant in support of his submission that the amendments sought were directly and unambiguously derivable from the application as filed, having regard to the common general knowledge that the notional skilled addressee would have possessed at the relevant date, took the form of affidavit evidence and excerpts from a number of textbooks.
- 2.2.4 The affidavit of Professor David H. Coy of the Department of Medicine of Tulane University could, on the face of it, be regarded as irrelevant, on the ground that it was given by a person who was too highly qualified to be regarded as a notional skilled addressee in what is, after all, a

well-developed technical field. However, even if the Board could accept that Professor Coy could properly be regarded as the notional, that is to say, average skilled person in the present field of chemistry of pyrimidines, the fact remains that the Board has only a single affidavit from a notional skilled addressee, and it cannot normally be the case that an affidavit by a single person suffices to discharge the burden of proof to the strict standard that is required (cf. above Section 2.2.2, third paragraph).

2.2.5 Turning next to the textbook evidence, namely documents (2) to (5), bearing in mind the observations set out above, the Board finds that there is insufficient nexus between what they, as a whole, state as regards the use of guanidine salts in general, as opposed to guanidine carbonate in particular. As was admitted by the Appellant, only three of the cited documents disclose the use of a ketoester as a starting compound, namely document (2) by way of reference to Ref. 19 (cf. the first paragraph on page 262 of (2)), document (3), line 8, and document (5), Table 2.2, and none of the cited documents describes the relevant reaction between a ketoester and a guanidine salt other than guanidine carbonate. Moreover, it is even indicated in Ref. 19 referred to in document (2), namely J. Am. Chem. Soc., 73 (1951), page 3763, that the condensation of certain ketoesters and guanidine failed entirely (cf. the left column on page 3763, lines 17 to 21). Also in document (5), which describes the "principal" or "common" synthesis of pyrimidines, that is, the condensation of a N-C-N fragment, such as urea, thioruea and guanidine, with a C-C-C fragment, such as a 1,3-dialdehyde, 1,3-diketone,  $\beta$ -ketoester,  $\beta$ -cyanoester, 1,3-diester and 1,3-dinitrile, it is disclosed that in practice many combinations of the above types of compound do not condense together to form the desired pyrimidine and that, because of the limitations of many reactions,

several simple substituted pyrimidines have still to be synthesized (cf. pages 20 to 25 under "(i) The Principal Synthetic Method", particularly page 21, the last two sentences of the right column).

It is true that general statements are made in the textbooks in relation to reactions of the general type involving the condensation of an N-C-N fragment with a C-C-C fragment, which are anyway too unspecified to give evidence for the specific reaction under consideration, but the issue of the allowability of the amendment under Article 123(2) EPC needs to be decided by reference to what can be derived from the patent application as filed in the light of common general knowledge and not vice versa.

2.2.6 Taking, therefore, the evidence as a whole, the Board finds that it is insufficient to discharge the burden of proof to the strict standard previously mentioned, and accordingly dismisses the Appellant's submission that the notional skilled addressee of the application in suit would have generalised "carbonates" to mean all salts.

2.3 Accordingly, in the Board's judgment, Claim 1 for Austria of the main request is not allowable, because its subject-matter does not meet the requirements of Article 123(2) EPC.

### 3. Auxiliary request

3.1 The claims according to this request correspond to those of the main request, except that in Claim 1 for Austria (Annex C) the starting compound "guanidine salt" is restricted to "guanidine carbonate". Therefore, the first question to be decided is, whether the subject-matter now claimed in Claim 1 for Austria, is allowable having regard to the provisions of Article 123(2) EPC.

3.2 Compared with the disclosure of the description of the present application as filed regarding the preparation of the desired compounds, namely, that a mixture of the appropriate  $\alpha$ -ketoester and guanidine carbonate in xylene is refluxed overnight, and the final product is then collected by filtration and purified (cf. page 5, lines 11 to 15, and the preparative examples), the subject-matter now being claimed only comprises a generalisation concerning the solvent, the reaction temperature, the reaction time and the separation of the end products. In particular, the specific solvent xylene is generalised to "an inert solvent"; the specific features relating to the reaction temperature and the reaction time are omitted and, finally, the particular measures for the separation of the end products are replaced by the general statement that "the product is retrieved".

3.2.1 Therefore, once more, the question is whether these generalisations would amend the present patent application in such a way that it contains subject-matter which extends beyond the content of the patent application as filed.

Applying the same approach as before to the present case, by reading the particular passage and the examples of the application as filed, it is the Board's judgment that the person skilled in the art would immediately understand that the use of xylene as a solvent, refluxing overnight and the separation of the product by filtration were merely typical examples of more general reaction conditions and, thus, not essential for the preparation of the desired compounds.

In respect of this particular point the Board itself possesses sufficient common general knowledge to justify this view, because it clearly belongs to the basic

knowledge of a chemist that a chemical reaction of the present type depends neither on the choice of a particular solvent as long as it is inert, nor on any specific reaction temperature or reaction time, as long as the desired reaction takes place, nor even on a certain method of separation of the end product.

- 3.2.2 In addition, further amendments in Claim 1 for the Contracting States other than Austria and in Claim 1 for Austria meet the requirements of Article 123(2) EPC. The definition of the alkyl and alkoxy radicals in that they contain less than 6 carbon atoms is based on the meaning of the expression "lower" indicated on page 1, lines 11 and 12, of the patent application as filed, and the disclaimer concerns the 8-alkoxy derivatives which are disclosed in document (1), column 1, lines 11 to 40.

4. Novelty

- 4.1 Since in the subject-matter now claimed the overlapping group of compounds disclosed in document (1) as set out below is disclaimed in its entirety, the novelty requirement under the EPC is clearly met.
- 4.2 The decision under appeal did not raise any novelty objection, and apparently held that by disclaiming the compounds described in Examples 1 and 11 of document (1) the subject-matter of both Claims 1 forming the basis of the decision under appeal the novelty requirement under the EPC was met.

However, according to the established jurisprudence of the Boards of Appeal, when examining novelty, the disclosure of a document has to be considered as a whole and not only on the basis of its examples (cf. for instance T 12/81, OJ EPO 1982, 296, paragraph 7 of the Reasons; T 666/89



(headnote published in OJ EPO 6/1992), paragraphs 5 to 7 of the Reasons and T 381/90 (unpublished), paragraphs 2.1 to 2.4 of the Reasons).

Moreover, for a selection of a group of compounds from a known class to be deemed novel, that selection has to add a new element to what is already known and hence involve a different technical teaching (cf. for instance T 12/90, reported in EPOR 5/1991, page 312, section 2.6 of the Reasons, and T 381/90, mentioned above, section 2.5 of the Reasons).

- 4.3 In the present case, document (1) discloses a group of compounds having the formula of Claim 1 for the Contracting States other than Austria set out in section I above, wherein X is  $-\text{CH}_2\text{CH}_2-$ , and  $\text{R}^3$  is in the 8-position and can represent hydrogen or an alkoxy radical (cf. column 1, lines 11 to 26). It also discloses that among the alkoxy radicals, especially lower alkoxy groups having less than 8 carbon atoms are preferred, such as methoxy, ethoxy, propyloxy, butyloxy and pentyloxy (cf. column 1, lines 27 to 40).

Accordingly, the Board finds that the technical teaching of this document makes available to the public compounds falling within the scope of Claim 1 of both sets of claims on which the decision under appeal was based, namely, the overlapping group of compounds wherein X is  $-\text{CH}_2\text{CH}_2-$ , and  $\text{R}^3$  in the 8-position is hydrogen or alkoxy. Thus, this overlapping group of compounds is considered to be merely a partial copy of what is already known and, therefore, does not provide any new technical teaching.

5. Remittal to the Examining Division under Article 111(1) EPC

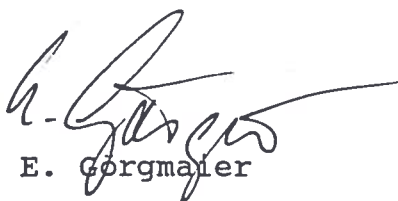
- 5.1 Although the Examining Division did not raise any objection with respect to inventive step, in the Board's view, the present application is still not ready for grant, because further examination of the amended and added sub-claims, as well as a number of small amendments in the description and in the claims, such as the correction of  $\alpha$ -ketoester in  $\beta$ -ketoester, appear to be necessary. Therefore, the Board exercises its power under Article 111(1) EPC and remits the case to the Examining Division for further prosecution.
- 5.2 In this connection the Board notes that - as in the case of both Claims 1 of Annexes A and C - the subject-matter of Claim 3 of Annex A and Claims 4, 8 and 9 of Annex C is precised by replacing the relative term "lower" by the number of carbon atoms and that in Claim 4 of Annex C the undue repetition of wording is avoided, so that these claims also meet the requirements of Article 84 in this respect.

Order

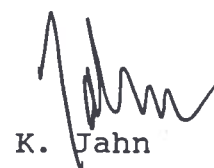
For these reasons, it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the Examining Division for further prosecution on the basis of the claims set out in Annex A and Annex C.

The Registrar:

  
E. Gorgmaier

The Chairman:

  
K. Jahn