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D E C I S I O N
of 24 May 2000

Case Number: T 0752/94 - 3.3.1

Application Number: 87307803.4

Publication Number: 0266042

IPC: C07D 475/04

Language of the proceedings: EN

Title of invention:
Optically active pteridine derivatives

Applicant:
University of Strathylcde

Opponent:
-

Headword:
Optically active pteridines/UNIVERSITY OF STRATHCLYDE

Relevant legal provisions:
EPC Art. 123(2), 84, 111(1)
EPC R. 29(6)

Keyword:
"Clarity within the meaning of Article 84 and Rule 29(6) EPC - main request, auxiliary requests I to V (no)"
"Support by the application as filed within the meaning of Article 123(2) EPC - auxiliary requests VI to XIX (no)"
"Remittal to the first instance - Article 111(1) - first instance bound by the ratio decidendi of its own decision - auxiliary request XX"

Decisions cited:
T 0150/82, T 0383/88

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0752/94 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 24 May 2000

Appellant: University of Strathclyde
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 29 April 1994 refusing European patent application No. 87 307 803.4 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. F. Ranguis
J. P. B. Seitz

Summary of Facts and Submissions

I. This appeal lies from the Examining Division's decision posted on 29 April 1994 refusing the European patent application No. 87 307 803.4 (Publication No. 0 266 042) on the ground that the then pending main, first, second and third auxiliary requests contained claims which did not comply with Articles 123(2), 54 and 56 EPC.

II. The main request contained twenty five claims, independent claims 1, 9 and 17 reading as follows:

"1. A process for the preparation of substantially pure (6R) or (6S) diastereoisomer of a derivative of tetrahydrofolic acid or a salt or ester thereof which process comprises the steps of:

(a) attaching a chiral auxiliary group at either N-5 or N-10 of a mixture of 6R and 6S diastereoisomers of tetrahydrofolic acid or of a substituted tetrahydrofolic acid or salt or ester thereof, so as to form a pair of new diastereoisomers, the chiral auxiliary group being (-) menthyloxycarbonyl, (-) bornyloxycarbonyl or (-) isobornyloxycarbonyl;

(b) separating the pair of new diastereoisomers and recovering the new diastereoisomers (6R or 6S) so formed corresponding to said desired (6R or 6S) diastereoisomer; and

(c) removing the chiral auxiliary group so as to convert the substantially pure new diastereoisomer so isolated into the corresponding desired substantially pure (6R) or (6S) diastereoisomer of a derivative of tetrahydrofolic acid or salt or ester thereof.

9. A pharmaceutical composition for therapeutic use, which comprises an amount, sufficient for the production of multiple therapeutically-effective doses thereof for the treatment of human beings, of a substantially pure pharmaceutically acceptable compound which comprises a (6S) diastereoisomer selected from the group consisting of 5-formyl-(6S)-tetrahydrofolic acid and pharmaceutically acceptable salts and esters thereof; wherein said substantially pure compound is a mixture of the (6S) and (6R) diastereoisomers and comprises greater than 90% by weight of the (6S) diastereoisomer, the balance of said substantially pure compound being the (6R) diastereoisomer; said amount of substantially pure pharmaceutically acceptable compound being at least 10.4g; in combination with a pharmaceutically acceptable carrier.

17. (6S) diastereoisomer of 5-formyl-tetrahydrofolic acid or a pharmaceutically acceptable salt or ester thereof, of diastereoisomeric purity greater than 90%, the balance being the (6R) diastereoisomer; for use in the manufacture of a medicament for the treatment of human beings, said medicament comprising a sufficient amount of said (6S) diastereoisomer for the production of multiple therapeutically-effective doses of said medicament, said combined amount of said (6S) and (6R) diastereoisomer being at least 10.4g."

III. The first auxiliary request contained eighteen claims, independent claims 1 and 17 being the same as the main request and independent claim 9 being limited to calcium 5-formyl-(6S)-tetrahydrofolate, each dose comprising up to 2000mg of a compound comprising more than 95% by weight of said pharmaceutically acceptable compound.

IV. The second auxiliary request contained seventeen claims, independent claims 1 and 9 being the same as the main request and independent claim 17 being limited to calcium 5-formyl-(6S)-tetrahydrofolate of purity greater than 95% and to doses each of them comprising up to 2000mg of said (6S) diastereoisomer.

V. The third auxiliary request contained nine claims, independent claim 1 being the same as that of the main request and independent claim 9 reading as follows:

"9. A pharmaceutical composition for therapeutic use produced as a result of separation by differential solubility in a polar solvent of a (6S) diastereoisomer from a mixture containing equal amounts of (6S) and (6R) diastereoisomers, characterised in that

(a) the composition comprises a therapeutically acceptable compound formed of the (6S) diastereoisomer of calcium 5-formyl-tetrahydrofolate in an amount greater than 95% by weight and the balance is formed of the (6R) diastereoisomer of calcium 5-formyl-tetrahydrofolate,

(b) the amount of the therapeutically acceptable compound is at least 10.4g, and

(c) the composition is in the form of multiple therapeutically-effective doses of up to 2000mg of the compound in combination with a pharmaceutically acceptable carrier for the treatment of human beings."

VI. In its decision, the Examining Division acknowledged the novelty and inventive step of the claims 1 to 8 of all the requests but held that the claims 9 to 25 of the main request, claims 9, 17 to 25 of the first auxiliary request, claims 9 to 17 of the second auxiliary request and claim 9 of the third auxiliary request did not satisfy the requirements of Article 123(2) EPC for at least one of the following reasons:

- the introduction of the 10.4g prepared in example 1 as a feature into composition and use claims was not unambiguously derivable from the application as filed given that example 1 from which this value is drawn out is a process example.

- this amount was only disclosed for the calcium salt and could not be generalised to any salt or ester.

- example 1 referred to scheme 4 wherein purity of 92% or 91% was disclosed.

- the dosage related to doses comprising up to 2000mg of said (6S) diastereoisomer was only disclosed in conjunction with the treatment of colorectal cancer.

VII. In the Statement of Grounds of Appeal, the Appellant abandoned the main request, maintained the first, second and third auxiliary requests and filed seven additional requests.

In response to a first communication of the Board, the Appellant abandoned the requests filed with the Statement of Grounds of Appeal and filed a main request and five auxiliary requests.

In response to a second communication of the Board attached to the summons to oral proceedings where the Appellant was informed that any other requests should be filed at the latest **one month** before the date of the oral proceedings, the Appellant abandoned the previous requests and filed a main request and twenty auxiliary requests received on 20 April 2000.

VIII. Independent claims 1 and 2 of the **main request** read as follows:

"1. A pharmaceutical composition for methotrexate rescue, which comprises substantially pure (as herein defined) calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate; the composition being in the form of an adult human daily dosage of 25 to 150mg of calcium 5-formyl-(6S)-tetrahydrofolate in combination with a pharmaceutically acceptable carrier, which is divided into multiple doses.

2. A pharmaceutical composition for treating colorectal cancer together with 5-fluorouracil, which comprises substantially pure (as herein defined) calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium

5-formyl-(6R)-tetrahydrofolate; the composition being in the form of an adult human daily dosage of 200 to 2000mg of calcium 5-formyl-(6S)-tetrahydrofolate in combination with a pharmaceutically acceptable carrier, which is divided into multiple doses."

Independent claim 1 of the **first auxiliary request** is the same as claim 2 of the main request.

Independent claim 1 of the **second auxiliary request** is the same as claim 1 of the main request.

Independent claims 1 and 2 of the **third auxiliary request** differ respectively from the independent claims 1 and 2 of the main request by the insertion of an additional feature after the expression "the balance being calcium 5-formyl-(6R)-tetrahydrofolate;" which reads as follows:

"and which has been produced as a result of separation by their different solubility characteristics in a polar solvent of a (6S) diastereoisomer from a mixture containing equal amounts of (6S) and (6R) diastereoisomers;"

Independent claim 1 of the **fourth auxiliary request** is the same as claim 2 of the third auxiliary request.

Independent claim 1 of the **fifth auxiliary request** is the same as claim 1 of the third auxiliary request.

Independent claim 1 of the **sixth auxiliary request** reads as follows:

"1. A pharmaceutical composition which comprises an amount of 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate; in combination with a pharmaceutically acceptable carrier."

Independent claim 1 the **seventh auxiliary request** differs from the independent claim 1 of the sixth auxiliary request by the insertion of an additional feature after the expression "in combination with a pharmaceutically acceptable carrier" which reads as follows:

", the composition being in the form of multiple doses thereof for the treatment of human beings".

Independent claims 1 and 2 of the **eighth auxiliary request** read as follows:

"1. A pharmaceutical composition for methotrexate rescue, which comprises an amount of 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate; the composition being in the form of an adult human daily dosage of 25 to 150mg of calcium 5-formyl-(6S)-tetrahydrofolate in combination with a pharmaceutically acceptable carrier, which is divided into multiple doses.

2. A pharmaceutical composition for treating colorectal cancer together with 5-fluorouracil, which comprises an amount of 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate; the composition being in the form of an adult human daily dosage of 200 to 2000mg of calcium 5-formyl-(6S)-tetrahydrofolate in combination with a pharmaceutically acceptable carrier, which is divided into multiple doses."

Independent claim 1 of the **ninth auxiliary request** is the same as claim 2 of the eighth auxiliary request.

Independent claim 1 of the **tenth auxiliary request** is the same as claim 1 of the eighth auxiliary request.

Independent claim 1 of the **eleventh auxiliary request** differs from the independent claim 1 of the sixth auxiliary request by the insertion of an additional feature after the expression "the balance being calcium 5-formyl-(6R)-tetrahydrofolate;" which reads as follows:

"and which has been produced as a result of separation by their different solubility characteristics in a polar solvent of a (6S) diastereoisomer from a mixture containing equal amounts of (6S) and (6R) diastereoisomers;"

Independent claim 1 of the **twelfth auxiliary request** differs from the independent claim 1 of the seventh auxiliary request by the insertion of the same additional feature as in the eleventh auxiliary request.

Independent claims 1 and 2 of the **thirteenth auxiliary request** differ respectively from the independent claims 1 and 2 of the eighth auxiliary request by the insertion of the same additional feature as in the eleventh auxiliary request.

Independent claim 1 of the **fourteenth auxiliary request** corresponds to claim 2 of the thirteenth auxiliary request.

Independent claim 1 of the **fifteenth auxiliary request** is the same as claim 1 of the thirteenth auxiliary request.

Independent claims 1 and 2 of the **sixteenth auxiliary request** read as follows:

"1. Calcium 5-formyl tetrahydrofolic acid which comprises substantially pure (as herein defined) (6S) diastereoisomer thereof, the balance being the (6R) diastereoisomer; for use in the manufacture of a medicament for use together with a therapeutically effective amount of 5-fluorouracil in the treatment of colorectal cancer, the medicament being in the form of an adult daily dosage of 200 to 2000mg of said (6S) diastereoisomer divided into multiple doses.

2. Calcium 5-formyl tetrahydrofolic acid which comprises substantially pure (as herein defined) (6S) diastereoisomer thereof, the balance being the (6R) diastereoisomer; for use in the manufacture of a medicament for methotrexate rescue in the form of an adult human daily dosage of 25 to 150mg of said (6S) diastereoisomer divided into multiple doses."

Independent claims 1 and 2 of the **seventeenth auxiliary request** differ respectively from the independent claims 1 and 2 of the sixteenth auxiliary request by the insertion of an additional feature after the expression "the balance being calcium 5-formyl-(6R)-tetrahydrofolate;" which reads as follows:

"and which has been produced as a result of separation by their different solubility characteristics in a polar solvent of a (6S) diastereoisomer from a mixture containing equal amounts of (6S) and (6R) diastereoisomers;"

Independent claim 1 of the **eighteenth auxiliary request** reads as follows:

"1. Calcium 5-formyl tetrahydrofolic acid in an amount of 10.4g comprising 91% by weight of the (6S) diastereoisomer thereof, the balance being the (6R) diastereoisomer; for use in the manufacture of a medicament for the treatment of human beings, said medicament comprising a sufficient amount of said calcium 5-formyl tetrahydrofolic acid for the production of multiple therapeutically-effective doses of said medicament."

Independent claim 1 of the **nineteenth auxiliary request** differs from the independent claim 1 of the eighteenth auxiliary request by the insertion of an additional feature after the expression "the balance being the (6R)diastereoisomer;" which reads as follows:

"and which has been produced as a result of separation by their different solubility characteristics in a polar solvent of a (6S) diastereoisomer from a mixture

containing equal amounts of (6S) and (6R) diastereoisomers;".

Independent claim 1 of the **twentieth auxiliary request** reads as follows:

"1. A process for the preparation of substantially pure (6R) or (6S) diastereoisomer of a derivative of tetrahydrofolic acid or a salt or ester thereof which process comprises the steps of:

(a) attaching a chiral auxiliary group at either N-5 or N-10 of a mixture of 6R and 6S diastereoisomers of tetrahydrofolic acid or of a substituted tetrahydrofolic acid or salt or ester thereof, so as to form a pair of new diastereoisomers, the chiral auxiliary group being (-) menthyloxycarbonyl, (-) bornyloxycarbonyl or (-) isobornyloxycarbonyl;

(b) separating the pair of new diastereoisomers and recovering the new diastereoisomers (6R or 6S) so formed corresponding to said desired (6R or 6S) diastereoisomers; and

(c) removing the chiral auxiliary group so as to convert the substantially pure new diastereoisomer so isolated into the corresponding desired substantially pure (6R) or (6S) diastereoisomer of a derivative of tetrahydrofolic acid or salt or ester thereof.

and is the same as the claim 1 that the Examining Division found patentable (see points II and VI above)."

IX. Oral proceedings were held before the Board on 24 May 2000. At the beginning of the oral proceedings, the Board observed that the Appellant's attempt to formulate allowable claims directed, in particular, to pharmaceutical compositions, processes for their preparation, use and/or product claims for a specific chemical compound had led to the submission of not less than 30 different requests. In view of this and given that in the communication attached to the summons to oral proceedings, the Appellant was invited to file amended requests at the latest one month before the date of the oral proceedings, the Appellant's right to amend the claims was regarded as exhausted. Consequently, the Board was not prepared to accept any amendment of any of the claims submitted in the Appellant's letter dated 20 April 2000 as main and auxiliary requests 1 to 20 or to consider any fresh claim or request. The only claims to be addressed at the present hearing were thus the claims of the twenty one requests filed with the Appellant's letter dated 20 April 2000.

X. The Appellant's submissions both in the written proceedings and at the oral proceedings regarding the requirements of Articles 123(2) and 84 EPC concerning the pharmaceutical compositions or use claims of the main request or the auxiliary requests I to XIX can be summarised as follows:

- The expression "substantially pure (as herein defined) calcium 5-formyl-(6S)-tetrahydrofolate" was supported by the content of the application as filed (see claim 20 and page 7, lines 1 to 4). In addition, this expression was clear in view of the said parts of the application as filed and,

furthermore, was justified to render the claims concise.

- The expression "the balance being calcium 5-formyl-(6R)-tetrahydrofolate" is supported by the example 1 in relation with scheme 1, from which the person skilled in the art would have unambiguously derived that the reduction of folic acid with sodium borohydride created a mixture of (6R) and (6S) tetrahydrofolic acid diastereoisomers.

- The feature related to the daily dosages of 25 to 150mg or 200 to 2000mg divided into multiple doses was supported by the application page 8, line 26 to page 9, line 15. Those doses were standard doses and depended, as shown by the declaration of Doctor Soukop, on the dosage of the medicament administered and the pharmacokinetics in the individual.

- The feature related to the process of separation of the diastereoisomers was supported by the application as filed page 5, lines 12 to 17.

- The amount 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate was supported by example 1 in combination with scheme 4. In particular, example 1(v), page 13 of the application as filed disclosed the preparation of a first crop of calcium 5-formyl-(6S)-tetrahydrofolate (7.2g) and further crops totalling 3.2g. These crops come from the transformation of 5,10-Methenyl-(6R)

tetrahydrofolic acid chloride, itself coming from 5-(-) Menthyloxycarbonyl-(6S) tetrahydrofolic acid (91% isomerically pure) as starting product.

In addition, the Board questioned the alleged purity of 91% of 5,10-Methenyl-(6R) tetrahydrofolic acid chloride and, derived from that, the purity of the final crops collected totalizing 10.4g; firstly, it did not seem clear whether the starting 5-(-) Menthyloxycarbonyl-(6S) tetrahydrofolic acid had a purity of 91% or 92% (see scheme 4) and, secondly, it was also questionable whether the different crops of calcium 5-formyl-(6S)-tetrahydrofolate totalizing 10.4g all had a purity of 91%. The Appellant argued that this purity was given with some approximation but within acceptable limits.

- The use of calcium 5-formyl tetrahydrofolic acid which comprises substantially pure (as herein defined) (6S) diastereoisomer thereof, the balance being the (6R) diastereoisomer; for use in the manufacture of a medicament, was supported by either claim 21 or claim 22 as originally filed and the description, page 8, lines 21 to 24.

XI. The Appellant requested that the impugned decision be set aside and the case be remitted to the first instance for further prosecution on the basis of the main request or one of the auxiliary requests.

XII. At the end of the oral proceedings the decision of the Board was given orally.

Reasons for the Decision

1. The Appeal is admissible

2. *Main Request*

2.1 Compliance with Article 84 EPC and Rule 29(6) EPC

Article 84 EPC states, in particular, that the claims define the matter for which protection is sought; they shall be clear and concise. This article is complemented by Rule 29 EPC. As the matter for which protection is sought is defined by the claims, their drafting is therefore particularly important, because the scope of the protection in accordance with Article 69 is decided in accordance with the content of the claims. It must also be pointed out that the claims must be worded so that the person skilled in the art can understand what the technical contribution to the art is. These requirements are, in particular, important for the essential technical features.

In that context, the expression "substantially pure (as herein defined)" present in the claims 1 and 2 of this request does not satisfy the requirement of clarity of Article 84 EPC for this would create uncertainty in respect of the matter for which protection is sought as in the description this term is stated to refer to the purity of a diastereoisomer of greater than 75%, preferably greater than 80%, or 90%, and most preferably greater than 95% (see page 7, lines 1 to 4). The Appellant's arguments that the said expression is clarified by the statement in the description must thus be rejected as it is at variance with the facts.

Moreover, Article 84 EPC prescribes that the **claims** must be clear. Consequently, it is not admissible to remedy an unclarity of a term in the claims, i.e. substantially pure, by introducing a reference to the description even if the latter were free of any ambiguity. Indeed, Rule 29(6) states that claims shall not, except where absolutely necessary, rely, in respect of the technical features of the invention, on reference to the description. As the Appellant failed to show such exceptional circumstances, the Board considers that the present request contravenes Rule 29(6) EPC (see 150/82, OJ EPO, 1984, point 3 of the reasons). For those reasons the said claims are not clear within the meaning of Article 84 EPC.

The fact that the claims must also be concise does not preclude the mandatory requirement of clarity.

It is therefore the Board's conclusion that the present request does not meet the requirements of Article 84 EPC and Rule 29(6) EPC.

3. *Auxiliary requests I, II, III, IV, V*

3.1 Compliance with Article 84 EPC and Rule 29(6) EPC

Claim 1 of each of the auxiliary requests I, II, III, IV, V contain the same technical feature as claims 1 and 2 of the main request, i.e the expression "substantially pure (as herein defined)". Therefore, those auxiliary requests suffer from the same deficiency and are not allowable under Article 84 EPC and Rule 29(6) EPC for the reasons set out in point 2.1 above.

4. *Auxiliary request VI*

4.1 Compliance with Article 123(2) EPC - Fair basis

In the Board's judgment, an amount of 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate is not directly and unambiguously derivable from the content of the application as filed.

First, contrary to the view expressed by the Appellant, it is not clear from the example 1(v) that the starting 5,10-Methenyl-(6R) tetrahydrofolic acid chloride is 91% isomerically pure, as the only information given there is that 17.5g of substance are used without any indication of purity. Furthermore, the resulting calcium 5-formyl-(6S) tetrahydrofolate is obtained in several crops. There is no indication that the calcium 5-formyl-(6S) tetrahydrofolate of each crop has the same purity especially since "Scheme 4" referred to in example 1 shows a difference in purity between the first and second crop (91% and 92% respectively) and the application as filed contains nothing which would support the Appellant's allegation that purity was given with some approximation but within acceptable limits. The only concrete facts are that in the application as filed a clear distinction is made between a purity of 91% or 92% and that the first and second crops do not show the same purity. However, in order to be allowable, an amendment under Article 123(2) EPC must satisfy a rigorous standard, i.e. one equivalent to "beyond reasonable doubt" (see T 383/88 of 1 December 1992, point 2.2.2 of the Reasons, cited in the Case Law of the Boards of Appeal

of the European patent Office, 3rd edition 1998, page 225).

As the Appellant failed to show that the technical feature at stake has a proper basis in the application as filed, claim 1 of the present request contravenes Article 123(2) EPC and this request is therefore not allowable.

5. *Auxiliary requests VII, VIII, XI, X, XI, XII, XIII, XIV, XV, XVI, XVII, XVIII and XIX*

5.1 Compliance with Article 123(2) EPC - Fair basis

Claim 1 and, in addition, either claim 2 or 3 of the auxiliary requests VII, VIII, XI, X, XI, XII, XII, XIV, XV, XVI, XVII, XVIII and XIX contain the same technical feature as claim 1 of the sixth request, i.e the expression "an amount of 10.4g of calcium 5-formyl tetrahydrofolate comprising 91% by weight of calcium 5-formyl-(6S)-tetrahydrofolate, the balance being calcium 5-formyl-(6R)-tetrahydrofolate". Those auxiliary requests suffer the same deficiency as the latter and are therefore not allowable under Article 123(2) EPC for the reasons set out in point 4.1 above.

6. *Auxiliary request XX*

6.1 Article 111(1)- Remittal to the first instance

Claims 1 to 8 of the present request are identical to claims 1 to 8 which the Examining Division already found allowable in the decision under appeal (see point VI above).

Since the Appellant is not adversely affected by this acknowledgment, there is no need for the Board in the present situation to exercise any power under Article 111(1) EPC to deal with the subject-matter of said claims. It is therefore appropriate to remit the case for further prosecution to the first instance, which shall be bound by the ratio decidendi of its own decision with respect to the novelty and inventive step of said claims.

Order

For these reasons it is decided that:

1. The impugned decision is set aside.

2. The case is remitted to the first instance for further prosecution on the basis of Claims 1 to 8 of auxiliary request 20 filed with the letter dated 20 April 2000.

The Registrar: The Chairman:

N. Maslin A. Nuss