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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0548/91 - 3.3.2

D E C I S I O N of 5 July 1994
correcting error in the decision
of the Technical Board of Appeal 3.3.2
of 7 February 1994

Appellant: (Opponent 01)
ADIR
22, rue Garnier
F-92200 Neuilly-sur-Seine (FR)

Representative:
-

Appellant: (Opponent 02)
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D-31061 Alfeld (DE)

Representative:
ter Meer - Müller - Steinmeister & Partner
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D-81679 München (DE)

Other party: (Opponent 03)
Hoechst Aktiengesellschaft
Zentrale Patentabteilung
Gebäude F 821
D-65926 Frankfurt (DE)

Representative:
-

Respondent: (Proprietor of the patent)
Schering Corporation
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Kenilworth, New Jersey 07033 (US)

Representative:
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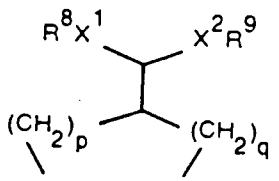
Patentanwälte
von Kreisler-Selting-Werner
Postfach 10 22 41
D-50462 Köln (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office dated 7 June 1991 concerning maintenance of European patent No. 0 050 800 in amended form.**

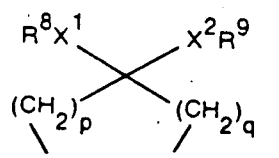
Composition of the Board:

Chairman: U.M. Kinkeldey
Members: I.A. Holliday
C.E.M. Holtz

In application of Rule 89 EPC the formula on page 3 defining the radical "V" is corrected to read:



The formula of the group "Q" on page 11 is corrected to read:



The Registrar:

P. Martorana

The Chairwoman:

U. Kinkeldey

BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

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D E C I S I O N
of 7 February 1994

Case Number: T 0548/91 - 3.3.2

Application Number: 81108348.4

Publication Number: 0050800

IPC: C07K 5/06

Language of the proceedings: EN

Title of invention:
Carboxyalkyl dipeptides, processes for their production and pharmaceutical compositions containing them

Patentee:
Schering Corporation

Opponent:
(01) ADIR
(02) Knappwost, Adolf, Professor Dr.
(03) Hoechst Aktiengesellschaft

Headword:
Dipeptides/SCHERING

Relevant legal norms:
EPC Art. 56, 83, 123

Keyword:
"Admissability of appeals"
"Appellant (01) - adversely affected (no)"
"Appellant (02) - man of straw (no)"
"Sufficiency of disclosure (yes)"
"Added subject-matter - no (after amendment)"
"Inventive step (yes) - no reasons to question the advantages demonstrated"

Decisions cited:
T 0244/85, T 0383/88, T 0635/88, T 0182/89, T 0299/89, T 0012/90, T 0289/91, T 0409/91, G 0001/84, G 0009/91

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

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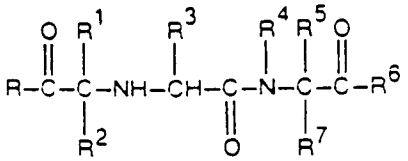
Composition of the Board:

Chairman: U.M. Kinkeldey
Members: I.A. Holliday
C.E.M. Holtz

Summary of Facts and Submissions

I. European patent No. 0 050 800 was granted on the basis of Claims 1 to 15 for the contracting states other than Austria and of Claims 1 to 14 for Austria contained in European patent application No. 81 108 348.4. Claim 1 reads as follows:

"1. A compound of the formula

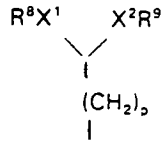


I

or a pharmaceutically acceptable salt thereof, wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenyloxy, dilower alkylamino lower alkoxy, acylamino lower alkoxy, acyloxy lower alkoxy, aryloxy, aryllower alkoxy, amino, lower alkylamino, dilower alkylamino, hydroxyamino, aryllower alkylamino, or substituted aryloxy or substituted aryllower alkoxy wherein the substituent is methyl, halo or methoxy; R^1 is hydrogen, alkyl of from 1 to 10 carbon atoms, substituted lower alkyl wherein the substituent is hydroxy, lower alkoxy, aryloxy, substituted aryloxy, heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, diloweralkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio, substituted arylthio, carboxy, carbamoyl, lower alkoxy carbonyl, aryl, substituted aryl, aralkyloxy, substituted aralkyloxy, aralkylthio or substituted aralkylthio, wherein the aryl or heteroaryl portion of said substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy, aralkylthio group is substituted with a group selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, carboxyl, cyano, or sulfamoyl; R^2 and R^7 are

the same or different and are hydrogen or lower alkyl; R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethylphenyl lower alkyl, hydroxyphenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl, amino lower alkyl, dimethylamino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, or lower alkyl thio lower alkyl; R^4 and R^5 are the same or different and are hydrogen, lower alkyl or Z, or R^4 and R^5 taken together form a group represented by Q, U, V, Y, D or E, wherein;

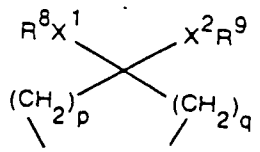
Z is



wherein X^1 and X^2 independent of each other are O, S or CH_2, R^8 and R^9 independent of each other are lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl having 3 to 8 carbon atoms, hydroxy lower alkyl, or $-(CH_2)_nAr$, wherein n is 0, 1, 2 or 3 and Ar is unsubstituted or substituted phenyl, furyl, thienyl or pyridyl, wherein said substituted phenyl, furyl, thienyl or pyridyl groups are substituted with at least one group that is independently selected from C_1 to C_4 alkyl, lower alkoxy, lower alkylthio, halo, CF_3 and hydroxy, or R^8 and R^9 taken together form a bridge W, wherein W is a single bond or a methylene bridge or a substituted methylene bridge when at least one of X^1 and X^2 is methylene, or W is an alkylene or substituted alkylene bridge having 2 or 3 carbon atoms, said substituted methylene bridge or said substituted alkylene bridge having one or two substituents selected from lower alkyl, aryl and aryl lower alkyl groups, and p is 0, 1 or 2; with the proviso that at least one of R^4 and R^5 is Z, with the proviso that if R^4 is Z and p is 0 then X^1 and X^2 must

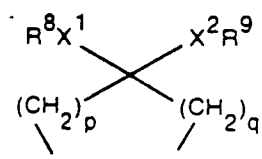
both be methylene, and with the proviso that if X^1 and X^2 are both methylene then R^8 and R^9 must form an alkylene bridge W;

Q is



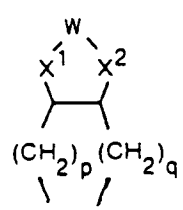
wherein R^8, R^9, X^1 and X^2 are as defined above, p is 0, 1 or 2, q is 0, 1 or 2, with the proviso that the sum of p and q must be 1, 2 or 3, with the proviso that if p is 0 then X^1 and X^2 must be methylene, and with the proviso that if X^1 and X^2 are methylene then R^8 and R^9 taken together form a bridge W, wherein W is as defined above;

V is



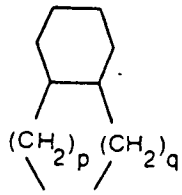
wherein R^8, R^9, X^1 and X^2 are as defined above, p is 0, 1 or 2 and q is 0, 1 or 2, with the proviso that the sum of p and q is 1, 2 or 3, with the proviso that if X^1 and X^2 are CH_2 then R^8 and R^9 taken together form a bridge W, wherein W is as defined above;

U is

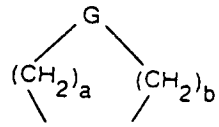


wherein W is as defined above (except that W may also be a methylene bridge when X^1 and X^2 are oxygen or sulfur), X^1 and X^2 are as defined above, p is 0, 1 or 2, q is 0,

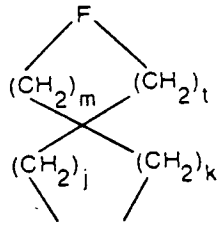
1 or 2, with the proviso that the sum of p and q is 1 or 2, and with the proviso that if p is 0, X^1 must be CH_2, excluding compounds wherein U is



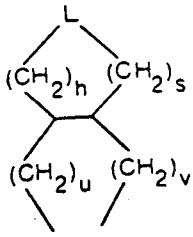
wherein p is zero or 1 and q is 1;
Y is



wherein G is oxygen, sulfur or CH_2, a is 2, 3 or 4 and b is 1, 2, 3, 4 or 5, with the proviso that the sum of a and b is 5, 6 or 7 or G is CH_2, a is 0, 1, 2 or 3, b is 0, 1, 2 or 3 with the proviso that the sum of a and b is 1, 2 or 3, with the proviso that the sum of a and b may be 1, 2 or 3 only if R^1 is lower alkyl substituted with aralkylthio or aralkyloxy;
D is



wherein F is O or S, j is 0, 1 or 2 and k is 0, 1 or 2, with the proviso that the sum of j and k must be 1, 2 or 3, and m is 1, 2 or 3 and t is 1, 2 or 3, with the proviso that the sum of m and t must be 2, 3 or 4;
E is



wherein L is 0 or S, u is 0, 1 or 2 and v is 0, 1 or 2, with the proviso that the sum of u and v must be 1 or 2, and h is 1 or 2 and s is 1 or 2, with the proviso that the sum of h and s must be 2 or 3."

Claim 1 for Austria related to a process for preparing the said compounds.

II. Three oppositions were filed against the granted patent.

Of the numerous documents cited during the Opposition Proceedings, the following remain relevant to the present decision:

(1) EP-A-0 012 401
(4) Federation Proceedings 38/13 (1979), p. 2779-2782,
(5) US-A-4 105 776
(8) FR-A-7 931 132

The Opposition Division maintained the patent on the basis of those claims submitted during Oral Proceedings. Claims 2 to 4 and 7 to 9 (for the Contracting States other than Austria) correspond word by word to granted Claims 2 to 4 and 7 to 9.

Granted Claim 10 was abandoned and claims 10 to 14 correspond to granted Claims 11 to 15.

Claim 1 was obtained from the corresponding granted Claim 1 through a limitation of the definition of groups Z and Y and through amendment of the definition of the group U (replacement of the expression "when X^1 and X^2 are oxygen or sulfur") by "or substituted methylene". In a similar way, Claims 1 to 13 for Austria were obtained from granted Claims 1 to 9 and 11 to 13 for Austria.

The Opposition Division considered the claimed subject-matter to be novel since neither document (1) nor any other available literature disclosed compounds presenting the obligatory disubstitution in the geminal position.

As to the question of inventive step, it was the view of the Opposition Division, that the closest prior art was document (1). In relation to (1), the problem underlying the contested patent was seen in developing ACE inhibiting substances having different excretion pathway.

The Opposition Division considered that the opposed patent represented a solution to the said problem and

- since the document (4) taught away from any bulky replacement or substitution of the C-terminal proline in ACE inhibitors in general,

- since surprising and advantageous effects had been established by means of comparative data,

- since document (8) disclosed C-terminal modifications in the Captopril skeleton but was silent regarding the excretion pathway and

- since there was no data pointing towards the two mentioned positive effects of the C-terminal introduction of a bulky amino acid derivative into the Captopril skeleton,

that the subject-matter of the patent in suit involved an inventive step.

The Examining Division further took the view that the objection of insufficient disclosure had not been sufficiently substantiated.

III. Appellant (O1) (ADIR) and Appellant (O2) (Knappwost) lodged appeals against the decision of the Opposition Division.

(a) Appellant (O1) objected to the contested patent on the grounds of insufficient disclosure (Art. 83 EPC) and requested the limitation of the patent to the examples 8-17 and 48-49.

In this respect, Appellant (O1) submitted a statement of an expert according to which the sufficiency of disclosure was questionable, at least for a part of the claimed subject-matter.

(b) Appellant (O2) requested the revocation of the contested patent for lack of novelty (Art. 54 EPC), inventive step (Art. 56 EPC) and sufficient disclosure (Art. 83 EPC).

Appellant (O2) argued that a novelty destroying overlap existed between those of the claimed compounds wherein R^4 and R^5 are connected together to form a disubstituted Q bridge and those compounds disclosed in document (1) and further that the ACE-inhibitory activity was obvious from the combined teaching of documents (1), (5) and (8).

The significance of the results of the *in-vivo* comparative tests provided by the Patentee in order to establish a preferential excretion pathway for the compounds of the patent at issue was also

contested; the results of such tests which had been carried out on dogs and rats were not necessarily transposable to the human being.

Finally it was objected that the disclosure of the patent was insufficient, particularly since a description of the process to be used in order to prepare some of the necessary starting products was missing and since some of the claimed compounds contained specific groups associated by one skilled in the art with pharmaceutical activities different from the intended activities. In support of these submissions Appellant (O2) filed documents (14) to (16) published after the priority date of the patent in suit.

(14) J. Med. Chem. 1988, 31, 875-885,

(15) Arzneim.-Forschung, Drug Res. 34 (II), Nr.10b (1984), 1435-1447

(16) Br. J. Clin. Pharmac. (1982), 14, 357-362

IV. The Respondent (proprietor of the patent) argued that the appeal by Appellants (O1) and (O2) were not admissible because the Appellant (O1) was not adversely affected (Art. 107 EPC) and Appellant (O2) appeared to be "a man of straw" (cf. T 635/88, OJ EPO 1993, 608, Reasons 8.3 and 8.4).

V. In a letter dated 17 May 1993, Appellant (O2) contested the doubts concerning his identity as a true opponent and informed the Board of Appeal that for personal reasons, he would no longer be active in the Opposition Proceedings.

A decision based on the state of the file was requested.

VI. The Board issued a communication on 19 January 1994, expressing a provisional opinion that the novelty of the subject-matter of Claim 1 as granted was destroyed by two overlaps existing with the subject-matter disclosed in document (1).
Decisions T 12/90 of 23 August 1990 (not published in OJ EPO; Reasons point 2.7) and T 383/88 of 1 December 1992 (not published in OJ EPO; Reasons point 4.2) were quoted.

VII. In reply, a new set of claims and a corresponding amended description were submitted by the Respondent with his letter of 28 January 1994. Additionally, the formula on the top of page 5 (lines 5-13) was amended. New Claim 1 has been obtained from Claim 1 previously submitted during the Oral Proceedings before the Opposition Division by:

- deleting the possibilities for R^4, R^5 taken together to form a group represented by V, Y, D and E,

- deleting the possibility for R^4, R^5 to be an hydrogen, a lower alkyl or a group Z and

- deleting the possibility for R^4, R^5 taken together to represent Q wherein R^8, R^9 are not bounded together.

In other words, Claim 1 was limited such that the substituents R^4, R^5 taken together form a group represented only by Q and U.

VIII. Oral Proceedings took place on 7 February 1994; Appellants (O1) and (O2) announced that they would not attend.

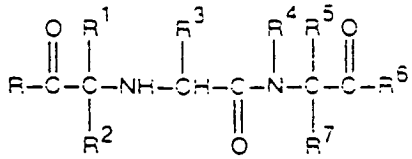
IX. The following questions were discussed at the Oral Proceedings:

- admissibility of the appeal of Appellant (O1),
- admissibility of the opposition and consequently of the appeal of Appellant (O2),
- admissibility of the newly filed claims with regard to Article 123(2) and 123(3) EPC,
- sufficiency of disclosure and support of the newly filed claims with regard to Articles 83 and 84 EPC,
- novelty and the inventive step of the newly filed claims, Articles 54 and 56 EPC.

In the course of the Oral Proceedings, the Respondent filed new claims (both sets for all states) in which the radical W was redefined to meet an objection under Article 123(2) EPC raised by the Board.

Claim 1 for the contracting states other than Austria now reads as follows:

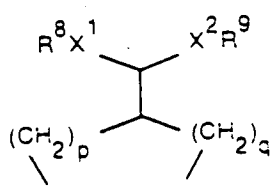
"1. A compound of the formula



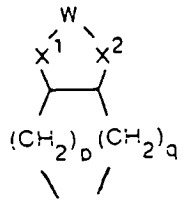
I

or a pharmaceutically acceptable salt thereof, wherein R and R^6 are the same or different and are hydroxy, lower alkoxy, lower alkenyloxy, dilower alkylamino lower alkoxy, acylamino lower alkoxy, acyloxy lower alkoxy, aryloxy, aryllower alkoxy, amino, lower alkylamino, dilower alkylamino, hydroxyamino, aryllower alkylamino, or substituted aryloxy or substituted aryllower alkoxy wherein the substituent is methyl, halo or methoxy; R^1 is hydrogen, alkyl of from 1 to 10 carbon atoms, substituted lower alkyl wherein the substituent is hydroxy, lower alkoxy, aryloxy, substituted aryloxy,

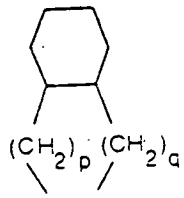
heteroaryloxy, substituted heteroaryloxy, amino, lower alkylamino, diloweralkylamino, acylamino, arylamino, substituted arylamino, guanidino, imidazolyl, indolyl, lower alkylthio, arylthio, substituted arylthio, carboxy, carbamoyl, lower alkoxy carbonyl, aryl, substituted aryl, aralkyloxy, substituted aralkyloxy, aralkylthio or substituted aralkylthio, wherein the aryl or heteroaryl portion of said substituted aryloxy, heteroaryloxy, arylamino, arylthio, aryl, aralkyloxy, aralkylthio group is substituted with a group selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, aminomethyl, carboxyl, cyano, or sulfamoyl; R^2 and R^7 are the same or different and are hydrogen or lower alkyl; R^3 is hydrogen, lower alkyl, phenyl lower alkyl, aminomethylphenyl lower alkyl, hydroxyphenyl lower alkyl, hydroxy lower alkyl, acylamino lower alkyl, amino lower alkyl, dimethylamino lower alkyl, guanidino lower alkyl, imidazolyl lower alkyl, indolyl lower alkyl, or lower alkyl thio lower alkyl; R^4 and R^5 taken together form a group represented by Q or U, wherein Q is



wherein X^1 and X^2 independent of each other are O, S or CH_2, R^8 and R^9 taken together form a bridge W, wherein W is an alkylene or substituted alkylene bridge having 2 or 3 carbon atoms, said substituted alkylene bridge having one or two substituents selected from lower alkyl, aryl and aryl lower alkyl groups, p is 0, 1 or 2, q is 0, 1 or 2, with the proviso that the sum of p and q must be 1, 2 or 3, with the proviso that if p is 0 then X^1 and X^2 must be methylene;

U is 

wherein W is a methylene bridge or a substituted methylene bridge when at least one of X^1 and X^2 is methylene, or W is an alkylene or substituted alkylene bridge having 2 or 3 carbon atoms, said substituted methylene bridge or said substituted alkylene bridge having one or two substituents selected from lower alkyl, aryl and aryl lower alkyl groups, (except that W may also be a methylene bridge when X^1 and X^2 are oxygen or sulfur), X^1 and X^2 are as defined above, p is 0, 1 or 2, q is 0, 1 or 2, with the proviso that the sum of p and q is 1 or 2, and with the proviso that if p is 0, X^1 must be CH_2, excluding compounds wherein U is



wherein p is zero or 1 and q is 1.

Claim 1 for Austria relates to a process for preparing the said compounds.

X. Appellant O1 requested that the decision under appeal be set aside and that the European patent No. 0 050 800 be limited to examples 8-17 and 48-49, and Appellant O2 requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

The Respondent requested that:

(1) The appeal by Appellant O1 be rejected as inadmissible,

(2) the appeal by Appellant O2 be dismissed and

(3) the patent be maintained on the basis of Claims 2-11 (for all designated States except Austria) and Claims 2-10 for Austria as filed on 28 January 1994 and Claim 1 (2 sets) as submitted in the Oral Proceedings and a description as filed on 28 January 1994, except for pages 3, 5, 26 and 27, submitted in the Oral Proceedings.

Reasons for the Decision

1. *Admissibility of the appeals*

1.1 Appellant (O1)

Under Article 107 EPC, the admissibility of the appeal by Appellant (O1) is *inter alia* dependant upon whether the party is adversely affected by the contested decision. In the statement of opposition, this Appellant requested the revocation of the patent merely because of lack of novelty of Claim 5 as granted. The Respondent amended this claim so that Appellant (O1) expressed satisfaction (see the letter dated 16 November 1988). Therefore, the Board considers the objection having been submitted in the notice of opposition against Claim 5 no longer relevant. There is jurisprudence by the Boards of Appeal (e.g. T 244/85 OJ EPO 1988, 216) that an Opponent, who does not disapprove the text in which it was intended to maintain a European patent in amended form, is not adversely affected. This applies especially to a situation like the present one where Appellant (O1) expressed satisfaction with Claim 5 as amended. Accordingly, the Appellant (O1) had a right to appeal

only to the extent of his original request (see also decision T 299/89 of 31 January 1991, not published in the OJ EPO).

Further, the Board draws attention to the Enlarged Board's decision G 9/91 (published in OJ EPO 1993, 408) which ruled that an opposition may not be extended after the term for filing the opposition has expired:

"The power of an Opposition Division or a Board of Appeal to examine and decide on the maintenance of a European patent under Articles 101 and 102 EPC depends upon the extent to which the patent is opposed in the notice of opposition pursuant to Rule 55(c) EPC."

Thus, Appellant (O1) may not introduce on appeal new grounds for opposition, i.e. insufficient disclosure. Thus, Appellant (O1) cannot be considered to be adversely affected within the meaning of Article 107 EPC nor can it extend its opposition beyond the objection to novelty of Claim 5 and consequently this appeal is inadmissible.

1.2 Appellant (O2)

The notice of appeal, the grounds of appeal and the appeal fee having all been submitted in due time, the appeal of Appellant O2 would be admissible, but for the objection raised in the Appeal Proceedings against his opposition.

1.2.1 The Respondent argues that the identity as true Opponent is in doubt. In support of this contention and of their request for a sworn statement from Appellant O2 that he is indeed acting on his own behalf, the Respondent invokes a lack of interest, referring inter alia to the Appellant's technical and professional background, his

age, the age of his wife and to his wife's professional background, implying that Appellant O2 cannot be the true Opponent.

During the Oral Proceedings, however, their request for a sworn statement by Appellant O2 to clear the identity issue was withdrawn.

1.2.2 It should be noted that the Respondent does not claim that an Opponent has to show any particular interest under the EPC in order to have the opposition examined on its merits. All the references with regard to the Appellant's personal circumstances were made to support the request for a sworn statement to clear the alleged identity question.

1.2.3 The Board wants to point out that the identity issue must be distinguished from issues related to particular legal requirements to be met by a party in order to render a suit brought by that party admissible. Under a particular piece of legislation, a party might not be qualified to raise an issue before a court of law, unless he shows a specific interest in bringing the suit, *legitimatio ad causam*.

Under the EPC, however, no such requirement is given, cf. Article 99 EPC, which states that "any person may give notice.... of opposition....". The words "any person" have always been understood as not requiring Opponents to state any particular interest or to qualify themselves in any respect. G 1/84, OJ EPO 1985, 299, confirmed this view in stating that "The motives of the opponent are in principle irrelevant (otherwise, no doubt, the phrase "any person" would have been rendered as "any person interested", whilst his identity is of primary procedural importance." (point 3 of the reasoning). In T 635/88 (OJ EPO 1993, 608) it was

further pointed out that "lack of interest in opposing a patent can not be considered as a ground of inadmissibility".

1.2.4 The facts related to the objections against Appellant O2 are essentially parallel to those in T 289/91, this Appellant being the same person in both cases. This Board concurs with the findings of T 289/91 that a minimum to be required from the objecting party requesting a sworn statement would be to point to concrete reasons to suspect that the Opponent in fact acted on behalf of a particular third party (see point 2.2.2 in that decision), and that Article 99 means that there is a presumption that any person who submits an opposition also acts on his own behalf (point 2.2.3).

1.2.5 It follows that there is no room for any further investigation, i.e. there is no reason to require a sworn statement from Appellant O2, nor can his opposition be rejected as inadmissible.

The opposition of Appellant O2 and consequently the appeal is therefore admissible.

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

2.1 The Board expressed doubts concerning the amended Claims 1 (both sets) submitted by the Patentee with the letter dated 28 January 1994, in particular the amendments made in the definition of U which was regarded as infringing the requirements of Article 123(2) and 123(3) in respect of the added and non-limiting expression **substituted**; in the definition of W, the expression "except that W may also be a methylene bridge when X^1 and X^2 are oxygen" as present in granted Claims 1, has been replaced by "except that W may also be a methylene bridge or substituted methylene

bridge". These amendments had already been submitted during the Opposition Proceedings. The said objections were overcome during the Oral Proceedings before the Board when the Respondent replaced the criticised expression by the following:

"wherein W is a methylene bridge or a substituted methylene bridge when at least one of X^1 and X^2 is methylene, or W is an alkylene or substituted alkylene bridge having 2 or 3 carbon atoms, said substituted methylene bridge or said substituted alkylene bridge having one or two substituents selected from lower alkyl, aryl and aryl lower alkyl groups, (except that W may also be a methylene bridge when X^1 and X^2 are oxygen or sulphur)".

The above amendment corresponds exactly to the scope of the granted Claims 1 and to the scope of Claims 1 as originally filed and is, therefore, in accordance with the requirements of Article 123(2) and (3) EPC.

2.2 The requested amendment of the formula on the top of page 5 (lines 5-13) of the description corresponds to the correction of an error that obviously occurred first at the printing stage and which results from a mistake on the part of the Office. Since the wording of the definition of the group Q first appearing on pages 2 and 3 of the description excludes the possibility for X^1 and X^2 to be attached at two different C-atoms, the correction of the formula is regarded by the Board as an obvious mistake whose correction does not contravene the requirements of Article 123 and of Rules 88 and 89 EPC.

2.3 Further deletion made in the description in order to exclude specific compounds no longer covered by the subject-matter of the claims and formal amendment carried out on line 1 of page 5 were also considered by the Board to satisfy the requirements of Article 123.

3. *Sufficiency of disclosure (Article 83 EPC)*

The Appeal is also concerned with the question of whether the disclosure of the disputed patent is sufficient to enable the skilled person to put the claimed invention into practice (Art. 83 or 100(b) EPC).

3.1 According to recent jurisprudence of the Boards of Appeal of the EPO, the disclosure of limited ways of performing the invention can be considered to be sufficient within the meaning of Article 83 EPC if it allows the man skilled in the art to perform the invention in the whole range that is claimed (see T 409/91 dated 18 March 1993, Reasons, point 2 to be published in the OJ EPO).

The question whether the disclosure of one way of performing the invention covers the whole claimed range is a question of fact that must be answered on the basis of the available evidence, and on the balance of probabilities in each individual case. The burden of proof in order to establish that the invention cannot be reproduced lies with the opponents who must establish that compounds covered by the claim cannot be prepared by routinely applying the disclosure of the original description or that they do not possess the expected property (cf. T 182/89, OJ 1991, 391).

3.2 In the present case, the claimed invention concerns carboxyalkyl dipeptides, their production and pharmaceutical compositions containing them. The claimed

dipeptides are defined by their chemical formula and by the lists of the corresponding chemical groups thereby considered. The description of the patent in suit generally discloses the processes to be used in order to prepare the claimed compounds. Specific examples illustrate methods of preparation and provide chemical and physical data of some of the dipeptides obtained thereby.

3.3 Appellant (O1) acknowledged in the letter of 3 October 1991 (see the statements made by the expert Mr. Lesieur) that at least for a main group of the claimed compounds of formula I, no particular difficulty would be encountered by the man skilled in the art when trying to prepare them. Furthermore, the Appellant, failed to provide any concrete evidence of unsuccessful laboratory attempts to prepare some of the claimed compounds when using the methods disclosed by the patent in suit.

3.4 Appelant (O2) also acknowledged in his letter of 9 February 1989 that at least for a part of the claimed compounds of formula I, no particular difficulty would be encountered by the man skilled in the art when trying to prepare them.

3.5 For the remaining compounds i.e. mainly for those compounds of formula (I) wherein R^4 and R^5 together form an optionally substituted heterocyclic system different from a 1,4-dithia-7-azaspiro[4.4]nonane or from an octahydrocyclopenta[b]pyrrole structure or for those compounds wherein R^4, R^5 independently represent original bulky heterocyclic groups, both Appellants stressed the insufficiency of disclosure. Opponent (O1) analysed the information from the available "literature" and stressed the insufficiency of disclosure. In this respect, it is to be noted that those particular compounds presented by

the Appellant (O1) (in the Annexe to the declaration of Mr. Lesieur) are no longer encompassed by the new limited claims submitted by the Respondent during the Oral Proceedings before the Board of appeal.

3.6 The second compound on page 14 is characterized *inter alia* by a C-geminal cyclobutyl group which, at least in respect of the steric hindrance, is comparable to a spiro group or to two C-geminal ethyl groups which according to the available experimental data appears appropriate in respect of the expected property.

However, Appellant (O2) failed to provide any concrete evidence of unsuccessful laboratory attempts to prepare some of the claimed compounds.

3.7 In the course of the Opposition Proceedings (letter of 13 March 1987), Opponent (O3) submitted a report of unsuccessful laboratory's attempts to reproduce those syntheses according to examples 5 and 20 of the patent in suit. However, after the Proprietor of the patent had provided further technical comments on the way the person skilled in the art could, with the help of the general technical knowledge in this technical field, successfully carry out the preparation of those compounds according to examples 5 and 20, Opponent (O3) appeared to be convinced since the latter neither contested the statements made by the Patentee's expert in this respect nor provided further evidence of insufficient disclosure.

3.8 Appellant (O2) finally contested the sufficiency of disclosure by arguing, that some of the claimed compounds possess some structural elements which would automatically confer to the corresponding compounds some undesirable properties. In the present case, this technical argument is not relevant, since it is part of

the common general knowledge in this technical field that some compounds with a complex structure exhibit simultaneously different pharmaceutical activities and insofar as Appellant (O2) failed to provide experimental data showing that the undesirable properties are preponderant over the desired property.

Further supplementary data submitted by the Respondent during Opposition and Appeal Proceedings further established the claimed activity for compounds of formula (I) obtained by using those methods presented in the description of the patent in suit.

3.9 Thus, in the present case, the Appellants failed to provide either "literature" or "experimental" evidence in order to challenge the sufficiency of disclosure of the newly limited but still exceptionally broadly claimed subject-matter. Accordingly, in the circumstances, the Board considers that the subject-matter according to the disputed patent satisfies the requirements of Article 83 EPC.

4. *Novelty (Article 54 EPC)*

Having regard to the limitation made by the Patentee to the claimed subject-matter immediately prior to the Oral Proceedings, the Board is now satisfied that the requirements of novelty are met. In any event, neither of the Appellants contested the novelty of the claimed subject-matter now on file.

5. *Problem and solution*

5.1 The patent in suit relates to carboxyalkyl dipeptides having ACE-inhibitory activity. The Board agrees with the Opposition Division that document (1) represents the

closest state of the art. Document (1) is also concerned with carboxyalkyl dipeptides of related general formula which exhibit ACE-inhibitory activity.

5.2 In relation to the prior art known from (1), the problem underlying the contested patent can be seen in developing ACE inhibiting substances with increased *in vitro* and *in vivo* activity, and secondly with a safer excretion pathway.

5.3 The problem of increased activity is solved by employing the carboxyalkyl dipeptides of Claim 1 of the patent in suit. Having regard to the comparative tests submitted by the Patentee during the Examining Proceedings with the letter dated 22 December 1983 and during the Opposition Proceedings with the letter of 30 June 1988 which show a significant improvement of the ACE-inhibitory activity, the Board is satisfied that this problem has indeed been solved.

5.4 The secondary problem of a safer excretion pathway appears to be solved for some of the claimed compounds as established by the experimental data submitted but not solved by other examples of the claimed compounds as stressed in paragraph 3 of the letter of 21 April 1992 by the Appellant (O2), in relation to the disclosure of documents (15) and (16). However, the fact (acknowledged by the Respondent) that the claimed compounds provide only a partial solution to the secondary problem does not prejudice the patentability of the claimed subject-matter as far as it is credible that substantially all of the claimed compounds represent an appropriate solution to the main problem underlying the patent in suit.

6. *Inventive step (Article 56 EPC)*

6.1 The essential difference between the compounds of Claim 1 and those disclosed in document (1) lies in the presence of a bulky cyclic substituent on the C-terminal proline group. In document (1), R^4 and R^5 may be connected together to form a methylene bridge of from 2 to 4 carbon atoms substituted by lower alkoxy or lower alkyl groups; in the disputed patent, the corresponding methylene bridge formed by R^4 and R^5 should be substituted by at least a saturated cyclic group.

6.2 Document (4) stresses that any bulky replacement of the C-terminal proline group should be avoided as unfavourable for maximal inhibitory activity. However, to some extent this "leading away" teaching of document (4) is rebutted by the disclosure of document (1) and also that of document (8), both published after the document (4) but before the priority date of the disputed patent. Documents (1) and (8) which in fact represent the most recent prior art before the priority date, disclose compounds with various degrees of structural similarity but all bearing a bulky substituent on the C-terminal proline group and exhibiting similar ACE inhibitory activity. Therefore, at the priority date, the person skilled in the art would no longer have considered document (4) as representing a particular prejudice against the provision of a bulky C-terminal group on the proline structure when searching for new carboxyalkyl dipeptides. Consequently, the person skilled in the art could have reasonably expected from documents (1) and (8), that the compounds according to claim 1 of the patent in suit would show the same kind and degree of activity.

6.3 Comparative data were, accordingly, an appropriate means to establish inventive step based on some unexpected property or some unexpected degree of activity.

The comparative data provided by the Respondent (see enclosure 1 submitted with the letter of 22 December 1983 and the comparative data submitted with the letter of 30 June 1988 and with the letter of 21 April 1992) established superior ACE-inhibitory activity over those compounds according to document (1) when the proline terminal group is replaced by a 1,4-dithia-7-azaspiro [4.4] nonane-8-carboxylic acid moiety or by an octahydro-cyclopenta[b]pyrrole-2(S)-carboxylic acid moiety.

Moreover, those comparative data reported by the Respondent in paragraph 2 of the letter of 21 April 1992, with reference to documents (15) and (16) established an unexpected preferential elimination pathway of some of the compounds according to the patent in suit when compared with compounds of document (1). Documents (15) and (16), both published after the filing date of the disputed patent, challenge the reliability of the latter comparative data in so far as they show, to some extent, that advantageous pharmacological activities established by means of data derived from experiments with animals, do not automatically occur in humans.

6.4 The Board is, however, of the view that inventive step is reasonably established by using experimental tools already available at the priority date of the disputed patent and generally considered at this time as reliable as far as the drug design is involved.

It is to be stressed that in the specific field of "drug design" any structural modification (even a minor modification in the stereochemical configuration of a compound) is "*a priori*", in the absence of any identified strong relationship between a specific structural element and pharmacological activity or in the absence of any established "bioisosterism", expected to disturb the pharmaceutical activity of the initial structure, particularly when the pharmaceutical activity involves an action on specific receptors.

Therefore, in the light of the superior activity and the preferential excretion pathway and in the absence of any evidence that some of the compounds comprised by the still very broad scope of the claim will not provide the unexpected properties, the Board acknowledges inventive step.

6.5 Had the Opponents submitted experimental evidence showing that at a representative selection of the multiplicity of the claimed compounds would not have exhibited the unexpected properties which form the basis for the acknowledgement of inventive step, the Board's conclusions in respect of the inventive step might possibly have been different.

6.6 It is to be noted that after limitation of the claimed subject-matter, document (8) appears to be as relevant as document (1). Those dipeptides disclosed in document (8) differ in the case wherein m=0 from those dipeptides according to the disputed patent in that at least one -S- bond has been replaced by a -NH- bond.

However, starting from document (8) as the closest prior art the same problems were to be solved and an analogous reasoning would have led to the same conclusion in respect of inventive step.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained on the basis of

   - Claims 2-11 for all designated States except Austria and Claims 2-10 for Austria, as filed on 28 January 1994, and

   - Claim 1 (2 sets) as submitted in the Oral Proceedings,

   - a description as filed on 28 January 1994, except pages 3, 5, 26 and 27 which were submitted in the Oral Proceedings.

The Registrar: The Chairman:

P. Martorana U. Kinkeldey