

Internal distribution code:

- (A) Publication in OJ
(B) To Chairmen and Members
(C) To Chairmen

D E C I S I O N
of 10 February 2000

Case Number: T 0285/95 - 3.3.1

Application Number: 90314319.6

Publication Number: 0437103

IPC: C07D 233/90

Language of the proceedings: EN

Title of invention:

Substituted 5-(alkyl)carboxamide imidazoles

Applicant:

SMITHKLINE BEECHAM CORPORATION

Opponent:

-

Headword:

Carboxamide imidazoles/SMITHKLINE BEECHAM

Relevant legal provisions:

EPC Art. 56, 116, 111(1), 123(2), 52(1)

Keyword:

"Inventive step (yes) - non-obvious solution"

Decisions cited:

G 0001/83

Catchword:

-



Europäisches
Patentamt

European
Patent Office

Office européen
des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Case Number: T 0285/95 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 10 February 2000

Appellant:

SMITHKLINE BEECHAM CORPORATION
One Franklin Plaza
P.O. Box 7929
Philadelphia
Pennsylvania 19101 (US)

Representative:

Thompson, Clive Beresford
SmithKline Beecham plc
Corporate Intellectual Property
Two New Horizons Court
Brentford
Middlesex TW8 9EP (GB)

Decision under appeal:

**Decision of the Examining Division of the
European Patent Office posted 9 November 1994
refusing European patent application
No. 90 314 319.6 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. The present appeal lies from the Examining Division's decision to refuse the European application No. 90 314 319.6 (publication number 0 437 103) on the ground that the subject-matter of the claims 1 to 10 for Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 10 for Contracting States ES and GR as originally filed did not involve an inventive step pursuant to Article 56 EPC in the light of the disclosure of the document:

(D) EP-A-0 324 377.

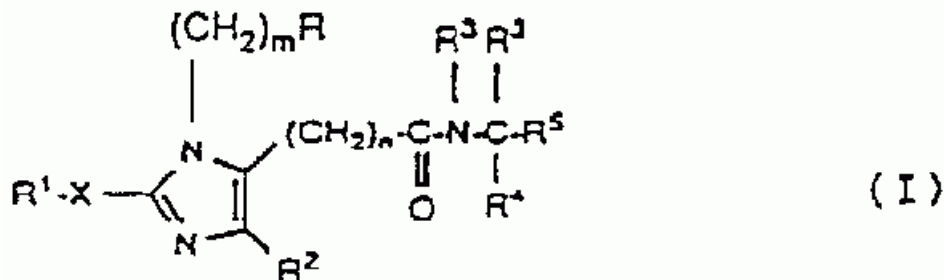
The Board will also refer to

(B) US-A-4 340 598

cited by the Examining Division in the first official communication.

II. Independent claim 1 for all the designated Contracting States other than ES and GR reads as follows:

"A compound of the formula:



in which:

R is adamantyl, or naphthyl, biphenyl, or phenyl, with each aryl group being unsubstituted or substituted by one to three substituents selected from halo, C₁₋₆alkyl,

C₁₋₆alkoxy, OH, CN, CO₂R³, tetrazol-5-yl, SO₃H, SO₂NHR³, NO₂, W, SC₁₋₆alkyl,

SO₂C₁₋₆alkyl, NHSO₂R³, PO(OR³)₂, CONR³R³, NR³R³, NR³COH, NR³COC₁₋₆alkyl, NR³CON(R³)₂, NR³COW, or SO₂W ;

R² is C₂₋₁₀alkyl, C₃₋₁₀alkenyl, (CH₂)₀₋₈C₃₋₆cycloalkyl, or (CH₂)₀₋₈phenyl unsubstituted or substituted by one to three substituents selected from C₁₋₆alkyl, C₁₋₆alkoxy, halo, OH, NO₂, NR³R³, W, CO₂R³, CN, CONR³R³, NR³COH, tetrazol-5-yl, NR³COC₁₋₆alkyl, NR³COW, SC₁₋₆alkyl, SO₂W, or SO₂C₁₋₆alkyl ;

X is a single bond, S, NR³, or O ;

m is 0-4 ;

R² is H, C₁₋₆alkyl, halo, W, CHO, CH₂OH, CO₂R³, CONR³R³, NO₂, CN, NR³R³, or phenyl;

each R³ independently is H or C₁₋₆alkyl;

R⁴ is H, C₁₋₈alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, tetrazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-,

isoxazolyl-Y-, or phenyl-Y-, with each aryl or heteroaryl group being unsubstituted or substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo, NR³R³, CO₂R³, OH, NO₂, SO₂NHR³, SO₃H, CONR³R³, W, SO₂W, SC₁₋₆alkyl, SO₂C₁₋₆alkyl, NR³C(O)H, NR³C(O)W, or NR³C(O)C₁₋₆alkyl ;

R⁵ is CO₂R³, CON³R³, or tetrazol-5-yl;

W is C_qF_{2q+1}, wherein q is 1-4 ;

Y is a single bond or C₁₋₆alkyl which is straight or branched; and

n is 0-5; or a pharmaceutically acceptable salt thereof."

Independent claim 6 relates to a compound according to any one of claims 1 to 5 for use as a medicament.

Independent claim 7 relates to a pharmaceutical composition which comprises a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

Independent claim 8 relates to a process for preparing a compound of the formula (I) or a pharmaceutically acceptable salt thereof as defined in claim 1.

Independent claims 9 and 10 relate to therapeutic use claims in the form as admitted by the Enlarged Board of Appeal (see G 1/83, OJ EPO 1985, 60) respectively for treatment of diseases in which angiotensin II receptor antagonism is a factor or for treatment of hypertension.

III. The Examining Division held that the solution to the

problem of providing further imidazole derivatives having angiotensin II receptor blocking activity resulting in antihypertensive properties was obvious in view of (D) since this document disclosed imidazole derivatives with angiotensin II receptor blocking activity differing from those claimed only in that, in document (D), the values of R¹⁸ and R¹⁹ of the substituent NR¹⁸R¹⁹ can be H, C₁₋₄alkyl, phenyl, benzyl, alpha-methylbenzyl, or taken together form a ring with the nitrogen atom, whereas for the claimed compounds, the alkyl chain, linked to the nitrogen atom, is methylene substituted by either an acid, an ester, an amide or a tetrazolyl.

According to the Examining Division, the performed modifications could not be regarded as "significant structural change" since the person skilled in the art by the mere reading of document (D) could see that the angiotensive II (AII) antagonistic activity was not linked to a specific substituent at the position 5 on the imidazole ring because they all could vary broadly without impairing this pharmaceutical property.

IV. The Appellant requested, by letter received on 3 December 1999 that the decision under appeal be set aside and

- as main request that the case be remitted to the Examining Division for further prosecution, and
- as auxiliary request that the case be remitted to the Examining Division for further prosecution on the basis of the claims 1 to 9 (respectively claims 1 to 9 for the Contracting States AT, BE,

CH, DE, DK, FR, GB, IT, LI, LU, NL, SE and claims 1 to 9 for the Contracting States ES and GR) all filed on 20 March 1995.

- oral proceedings under Article 116 EPC was requested, should the Board of Appeal be minded to make an adverse decision on the basis of the written submissions.

V. The Appellant, in his Statement of Grounds of appeal, submitted in essence that:

- the Examining Division erred in considering that the wide variety of substituents defined in (D) for R⁸ and R¹⁸ and R¹⁹ suggested that the nature of the substituent at position 5 was not critical to retaining the pharmacological activity. This was supported by the included experimental results comparing two compounds outside the scope of Formula (I) of the present application with two compounds which are within (Examples 1 and 12), using the *in vitro* assays described at page 19 and 20 of the application. From the tests presented, it resulted that for the compounds outside the scope of the claim 1, no IC₅₀'s or K_B's could be determined at the concentrations tested. Those tests showed that a relatively modest variation in the nature of the substituent at position 5 could lead to a serious loss of activity;
- the analysis of the Examining Division relied on the use of hindsight as it elected, from the vast array of possibilities offered by formula (I), the substituent value alleged to provide the

springboard for compounds of the claim 1. There is no teaching in (D) to suggest that a preferred value for R¹⁸ is methyl let alone that it should be substituted and that the closest prior art compound, should be one containing a morpholine ring;

- even if the skilled man had made the various selections suggested by the Examining Division and arrived at the N-alkyl substituent as a suitable starting point for further modification, to make further, new imidazole derivatives, he would have had a wide choice of possibilities. He would not be faced with a "one way" street or even a limited number of options. Though the person skilled in the art "could" have made each of these selections, the Examining Division failed to establish a case for "would".

Reasons for the Decision

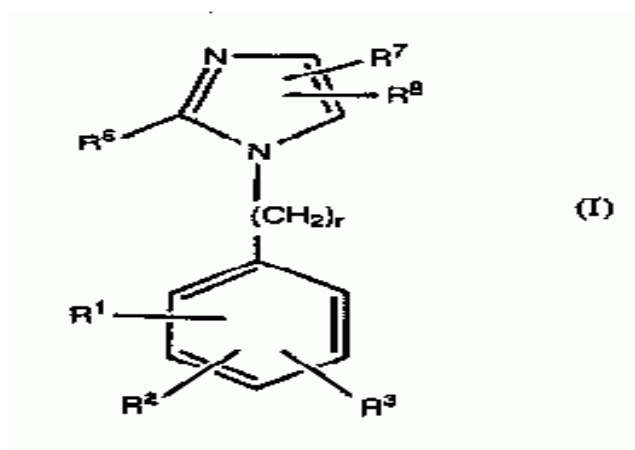
1. The appeal is admissible.

Main request

2. There are no objections under Article 123(2) EPC to the claims, which are those originally filed and to the amendments made on pages 8 and 9 of the application filed on 14 February 1997. These amendments correspond essentially to the subject matter of claims 8 and 9 as originally filed, i.e. that part of the claimed invention which refers to the medical use of the claimed compounds in accordance with the decision

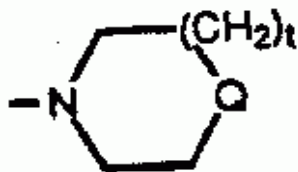
G 1/83 (op. cit).

3. After examination of the cited prior art, the Board has reached the conclusion that the claimed subject-matter of the present claims, is novel. Since in the decision under appeal the Examining Division acknowledged the novelty of the subject-matter of the present claims, it is not necessary to give detailed reasons for this finding.
4. It still remains to be decided whether the claimed subject-matter involves an inventive step.
- 4.1. The Board considers, in agreement with the Examining Division and the Appellant, that the closest prior art to the claimed invention is document (D) which relates to an angiotensin II receptor blocking imidazoles of formula:



wherein

R⁸ is $-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NR}^{18}\text{R}^{19}$, R¹⁸ and R¹⁹, independently being H, alkyl of 1 to 4 carbon atoms, phenyl, benzyl, alpha-methylbenzyl, or taken together with the nitrogen form a ring of the formula:



Q being NR²⁰, O or CH₂, R²⁰ being H, C₁-C₄ alkyl, phenyl, t being 0 or 1. The definitions given for the other groups R¹, R², R³, R⁶, R⁷ may be disregarded as they are not relevant for deciding the present case (see page 4, line 44 to page 11, line 45 and claim 1 of document (D)).

- 4.2. In the light of this closest state of the art, the technical problem underlying the application with respect to this subject-matter is to be seen in providing further imidazole derivatives which are angiotensin II (AII) receptor antagonists having anti-hypertensive activity.

According to the application this problem is essentially solved by replacing the substituent NR¹⁸R¹⁹ such as defined at point 4.1 above by a substituent NR³-CR³R⁴R⁵ chosen among those wherein R⁵ is CO₂R³, CONR³R³ or tetrazol-5-yl, R³ is independently H or C₁-C₆ alkyl and R⁴ is H, C₁₋₈alkyl, thienyl-Y-, furyl-Y-, pyrazolyl-Y-, imidazolyl-Y-, thiazolyl-Y-, pyridyl-Y-, tetrazolyl-Y-, pyrrolyl-Y-, triazolyl-Y-, oxazolyl-Y-, isoxazolyl-Y-, or phenyl-Y-, with each aryl or heteroaryl group being unsubstituted or substituted by C₁₋₆alkyl, C₁₋₆alkoxy, halo, NR³R³, CO₂R³, OH, NO₂, SO₂NHR³, SO₃H, CONR³R³, W, SO₂W, SC₁₋₆alkyl, SO₂C₁₋₆alkyl, NR³C(O)H, NR³C(O)W, or NR³C(O)C₁₋₆alkyl;

In view of the reported in vitro radio ligands tests submitted in annex I of the Statements of Grounds of appeal, related to the ability of claimed compounds N-[*]c1c[nH]c2c1C(=O)N(C)C2 (Example 1) and N-[*]c1c[nH]c2c1C(=O)N(C)C2 (Example 12) to compete with angiotensine II for binding to vascular angiotensin II receptors and to antagonize the contractile response to angiotensine II in the isolated rabbit aorta, the reported in vivo tests related to the inhibition of pressor response to exogeneous angiotensin II in conscious rats carried out with the compound N-[*]c1c[nH]c2c1C(=O)N(C)C2-L-phenylalanine (ex 14) and the information provided in the general description (in particular page 1, lines 12 to 24; page 21, line 22 to page 23, line 24), the Board is satisfied that the compounds as defined in claim 1 solve the said technical problem.

- 4.3. It remains to be decided whether or not the compounds of claim 1 of the application in suit meet the requirement of inventive step.

Referring to the compounds of document (D), the Examining Division stated on page 5 of the reasons:

"...the performed modifications, although carboxylic derivatives including tetrazolyl groups are introduced at the end of the chain attached at the position 5 of the imidazole ring, cannot be regarded as "significant structural change" given the person skilled in the art by the mere reading of document (D) could see that the

angiotensive II (AII) activity was not linked to a specific substituent at this same position 5 on the imidazole ring because they all could vary broadly without impairing this pharmaceutical property."

The Board disagrees that the document (D) would teach that the angiotensive II (AII) activity is not linked to a specific substituent at the position 5 on the imidazole ring. In the Board's view, the teaching of the document (D), certainly broad, is nevertheless more limited than that assessed by the Examining Division. Document (D) discloses that the compounds as defined at point 4.1 are angiotensin II receptor blocking agents. That does not mean that the teaching of this document is strictly limited to this disclosure (see below) ; nevertheless the generalization made by the Examining Division is not properly based. The Board found nowhere in (D) an indication that R^8 or even R^{18} or R^{19} stands for any substituent nor can this interpretation be derived from the list related to said substituents.

However, the Board does not agree that the Examining Division has relied on hindsight in having taken as starting product for its considerations the compounds of (D) which are the most structurally related to those presently claimed. A comparison by its very nature requires familiarity with the subject-matter of the application. Furthermore, to be relevant the comparison must relate to the compounds of the closest state of the art which possess maximum similarity with regard to structure and use.

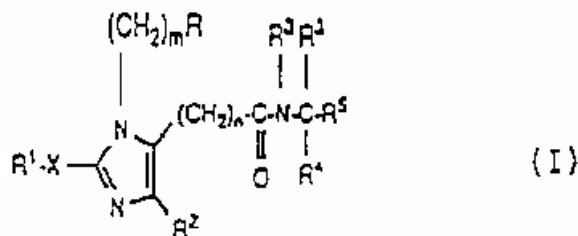
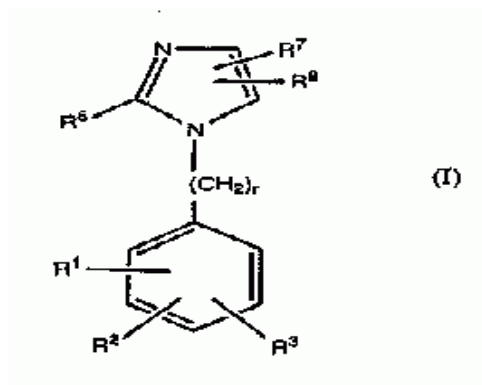
The Board's conclusion is therefore that the inventive step of the claimed compounds must be assessed in view

of the compounds of (D) wherein R¹⁸ or R¹⁹ is methyl (CH₂-**H**) or CH₂-C₁-C₃ **alkyl** or benzyl (CH₂- **phenyl**) and the question to be answered is whether the person skilled in the art would have been directed to vary the said substituents in such a manner that he would have considered the claimed compounds for providing angiotensin II antagonists. Incidentally, the Board notes that R¹⁸ and/or R¹⁹ are methyl in the compounds No. 134 and 135 of (D).

Schematically, the structural differences between document (D) and the claimed subject-matter may be represented as follows:

(D)

Claimed subject-
matter



R¹⁹

R⁸ is -(CH₂)_n-C(=O)N-R¹⁸

-CH₂-H

R³R³

-(CH₂)_n-C(=O)-N-C-R⁵

R⁴

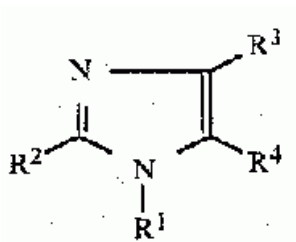
CH₂-CO₂R³

-CH ₂ -alk	CH ₂ -CONR ³ R ³
-CH ₂ -N	CH ₂ -tetrazol-5-yl
-CH-N	
CH ₃	

In other terms, document (D) discloses that the carbon in alpha of the amide linker may be a methyl group or may be a methyl group substituted by a lower alkyl group or a methyl group substituted by a phenyl group and the question is whether or not, in view of the cited prior art, it would have been obvious for the person skilled in the art to replace for an angiotensive II (AII) activity, on the carbon in alpha of the amide group, an hydrogen atom or a C₁-C₃ alkyl or a phenyl group (R¹⁸ or R¹⁹ of document (D)) by a substituent -R⁵ as defined in the claim 1 of the application in suit i.e. CO₂R³, CONR³R³ or tetrazol-5-yl.

In the Board's judgment, the person skilled in the art reading the disclosure of (D) would have understood that other alkyl, cycloalkyl or aryl groups could have been envisaged for R¹⁸ or R¹⁹. By contrast, the R⁵ substituents according to the application in suit result from a choice among carboxylic, carboxamid or tetrazol-5-yl substituents. This replacement goes beyond the teaching of (D) properly construed. In other words, there is no indication in document (D) which would have led the person skilled in the art to expect that the solution to the present technical problem would lie in the provision of compounds in which the substituent on the carbon atom in á of the amide linker is a carboxylic group, a C₁-C₆alkyl ester thereof, an amide group, a N- or N,N-C₁-C₆alkyl amide group or a tetrazol-5-yl group. Nor could document (B) have

completed the teaching of (D) to get to the present invention. Document (B) discloses hypotensive imidazole derivatives and addresses the same technical problem (see column 1, lines 4 to 27). It discloses compounds of the following formula:



wherein R^1 , R^2 , R^3 can be the same as the corresponding substituents of the claimed compounds and R^4 is $(CH_2)_n-CONH_2$. Therefore this document cannot give any relevant information to the person skilled in the art which would complete the teaching of document (D).

- 4.4 It follows from the above that the subject-matter of claim 1 for the designated Contracting States except Greece and Spain is not rendered obvious by document (D), either alone or in combination with document (B). Dependent claims 2 to 5 relating to specific embodiments of this invention, claim 6 directed to a compound of claim 1 for use as a medicament, claim 7 relating to a pharmaceutical composition, claim 8 relating to a process for the preparation of the compounds of claim 1, claims 9 and 10 directed to the use of a compound of claim 1 in the preparation of medicament are based on the same inventive concept and derive their patentability from that of claim 1, as do claims 1 to 10 for Greece and Spain.

4.5 Although the Board has come to the conclusion that the claimed subject-matter complies with the requirements of the Article 52(1) EPC, it was noted that the document (D) i.e. the closest prior art was not acknowledged in the description. Therefore, having regard to the fact that the function of the Boards of Appeal is primarily to give a judicial decision upon the correctness of the earlier decision taken by the first instance, the Board makes use of its competence under Article 111(1) EPC and remits the case to the first instance for further prosecution.

5. It follows from the above that the Appellant's auxiliary request need not be examined.

In the absence of an adverse decision, the condition attached to the Appellant's request for oral proceedings is not met and oral proceedings are not necessary.

6. The Board has incidentally noted that in claim 1 of the published European patent application EP-A-0 437 103, R⁵ may be "CON³R³" which would seem to be an erroneous reproduction of the substituent "CONR³R³" disclosed in the said document on page 5, line 8 as well as in the application as filed on page 7, line 17 and in claim 1 on page 64, line 4. This is a matter to be dealt with by the Examining Division when resuming the examination (see point 4.5 above).

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.

The Registrar:

The Chairman:

E. Görgmaier

A. Nuss