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D E C I S I O N
of 22 April 2002

Case Number: T 0126/99 - 3.3.1

Application Number: 93918407.3

Publication Number: 0652874

IPC: C07D 403/04

Language of the proceedings: EN

Title of invention:

2-Heterocyclic-5-Hydroxy-1,3-Pyrimidines useful as
antiinflammatory agents

Applicant:

WARNER-LAMBERT COMPANY

Opponent:

-

Headword:

Pyrimidinol-imidazole/WARNER-LAMBERT COMPANY

Relevant legal provisions:

EPC Art. 83, 56
EPC R. 88

Keyword:

"Correction of the description as originally filed - admitted
(yes) - obvious error"
"Inventive step (yes) - non obvious solution"

Decisions cited:

G 0003/89; G 0011/01; T 0493/90; T 0939/92; T 0964/92;

Catchword:

-



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Boards of Appeal

Chambres de recours

Case Number: T 0126/99 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 22 April 2002

Appellant: WARNER LAMBERT COMPANY
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Ann Arbor
Michigan 48105 (US)

Representative: Mansman, Ivo
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 9 September 1998
refusing European patent application
No. 93 918 407.3 pursuant to Article 97(1) EPC.

Composition of the Board:

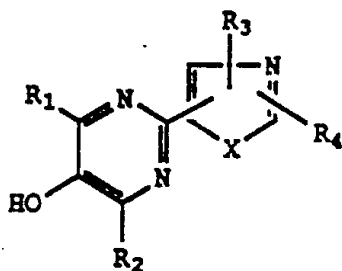
Chairman: P. P. Bracke
Members: P. F. Ranguis
J. P. B. Seitz

Summary of Facts and Submissions

I. This appeal lies from the Examining Division's decision refusing the European patent application No. 93 918 407.3 (Publication No. 0 652 874) on the ground that the subject-matter of the then pending request (the set of claims filed on 16 January 1998) did not involve an inventive step.

II. Said request contained nine claims, independent Claims 1 and 6 to 8, reading as follows:

"1. A compound of the formula



I

or a pharmaceutically acceptable salt or hydrate thereof, wherein

X is NH,

R₁ and R₂ are each independently hydrogen or C₁-C₆ alkyl;

R₃ is hydrogen, C₁-C₆ alkyl, NR₅R₆, wherein R₅ and R₆ are each independently hydrogen or C₁-C₆ alkyl, OR₇ in which R₇ is hydrogen, C₁-C₆ alkyl or phenyl, phenyl, substituted phenyl wherein the phenyl is substituted by one, two or three substituents selected from C₁-C₄

alkyl, C₁-C₆ alkoxy, C₁-C₆ thioalkoxy, C₁-C₆ alkanoyloxy, C₁-C₆ carboalkoxy, hydroxymethyl or NR₅R₆ wherein R₅ and R₆ have the above meaning, nitro, trifluoromethyl or halogen selected from fluoro, chloro or bromo;

R₄ is phenyl or substituted phenyl, wherein substituted phenyl is as defined above for R₃, NR₅R₆ wherein R₅ and R₆ are as defined above, OR₇ wherein R₇ is as defined above".

"6. A pharmaceutical composition which comprises an amount of a compound according to claims 1 to 5 and a pharmaceutically acceptable carrier".

"7. Use of a compound of claims 1 to 5 for the manufacture of pharmaceuticals for treating a condition advantageously affected by the inhibition of one of 5-lipoxygenase and cyclooxygenase or both 5-lipoxygenase and cyclooxygenase in a human suffering from the condition".

"8. Use of a compound of claims 1 to 5 for the manufacture of pharmaceuticals for treating inflammation, allergy and ulcers in a human in need of such treatment".

III. The following documents were cited in the examining proceedings:

(1) EP-A-0 164 765

(2) EP-A-0 449 211

(3) EP-A-0 371 438

The Examining Division held that, starting from document (1) as the closest state of the art, the technical problem to be solved was to provide further compounds which inhibited prostaglandin formation and had activity as lipoxygenase inhibitors. The person skilled in the art would not have arrived at the claimed compounds in view of the structural differences between the claimed compounds and those of document (1). However, it had not been made credible that all members or substantially all members of the claimed group of compounds solved the technical problem and thereby made a technical contribution to the art for an inventive step to be acknowledged.

IV. With the statement of grounds of appeal, the Appellant argued that the aim of the claimed invention was to provide a new group of compounds having activity as inhibitors of 5-lipoxygenase and/or cyclooxygenase and, therefore, providing treatment of conditions advantageously affected by such inhibition. Having regard to Example 6, which had been tested positive, it was credible that the problem had been solved. None of the cited documents suggested that the claimed compounds would have represented an incentive for a skilled person to envisage that the specific 2-imidazol (derivatives)-5-hydroxy-1,3-pyrimidines would have solved the technical problem.

V. In a communication accompanying the summons to oral proceedings scheduled on 22 April 2002, the Board raised doubts concerning the possibility of synthesizing all the encompassed compounds of formula (I) having regard to the mode of synthesis disclosed in the description which would be contrary to the requirements of Articles 83 and 84 EPC.

VI. In response, the Appellant contested the preliminary opinion of the Board and filed in support two documents representing the technical general knowledge:

(4) Beyer Walter; Lehrbuch der Organischen Chemie, 1988, 21. Aufl., page 742

(5) Romps Chemie Lexikon, 7. Aufl., 1973, page 1566 to 1567

and argued that it was common general knowledge to prepare mono-, di- or trisubstituted imidazoles, substituted at its C-atoms, by a condensation of α -halocarbonyl-compounds with amidines as disclosed on page 14, lines 17 to 20 of the application as filed. Furthermore, the scheme set out on page 21 of the application as filed showed the preparation of one embodiment of the invention with a hydroxy-moiety in position -2.

The Appellant also filed four auxiliary requests (cf. point 7 below).

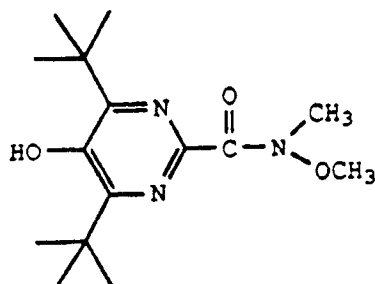
VII. The Appellant requested that the contested decision be set aside and that the case be remitted to the first instance with the order to grant a patent on the basis of Claims 1 to 9 of the main request and a description yet to be amended.

VIII. Oral proceedings were cancelled and the present decision was taken in the written procedure.

Reasons for the Decision

1. The appeal is admissible
2. *Correction under Rule 88 EPC*
 - 2.1 The parts of a European patent application or of a European patent relating to the disclosure (the description, claims and drawings) may be corrected under Rule 88, second sentence, EPC only within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed. Such a correction is of a strictly declaratory nature and thus does not infringe the prohibition of extension under Article 123(2) EPC (cf. the conclusion of G 3/89, OJ EPO 1993, 117 and the order of G 11/91, OJ EPO 1993, 125).
 - 2.2 In the communication of 16 August 1996, the Examining Division had held that there seemed to be an error on page 9 of the description in that it was indicated that "Compound of example No. 1" had been tested. In his response of 18 February 1997, the Applicant (now Appellant) had submitted that the biological results in the table of page 9 obviously relied on the only active compound of Example 6".
 - 2.3 In order for a correction under Rule 88, second sentence, EPC to be allowable, it must be established (a) that an error is in fact present in the document filed at the EPO, and (b) that the correction of the error is obvious in the sense that it is immediately evident that nothing else would have been intended than what is offered as the correction (see T 493/90 of 10 December 1991, point 2 of the reasons).

2.4 Example No. 1 relates to the preparation of 4,6-bis-(1,1-dimethylethyl)-5-hydroxy-N-methoxy-N-methyl-2-pyrimidinecarboxamide, an intermediate product of formula



This compound is not a product according to the invention and the Board finds, in agreement with the Examining Division, that an error is without doubt present. Furthermore, since the sole exemplified compound falling within the scope of the pharmaceutical compounds as defined in the application as filed is the 4,6-bis(1,1-dimethylethyl)-2-(2-hydroxy-5-methyl-1H-imidazol-4-yl)-5-pyrimidinol, i.e. compound No. 6 and since this compound was originally and individually claimed (cf. Claim 5), it is immediately evident that compound No. 6 was tested instead of compound No. 1. Therefore, correction on page 9, line 25 of the Figure "1" by the Figure "6" is allowed according to Rule 88 EPC.

Main request

3. *Article 123(2) EPC*

The Board is satisfied that the present set of claims

has not been amended in such a way that it extends the subject matter of the application as filed. In particular:

- Claim 1 finds support on page 2, lines 10 to 26 and page 3, lines 24 to 35 of the application as filed,
- Claims 6 and 7 find support on page 2, line 27 to page 3, line 12 of the application as filed,
- Claim 8 finds support on page 1, lines 17 to 19 and on page 3, lines 2 to 3 of the application as filed,
- Claim 9 finds support in Claim 12 of the application as filed.

Dependent Claims 2 to 5 correspond to Claims 2 to 5 as filed.

This was not contested by the Examining Division.

4. *Article 83 EPC*

4.1 In view of the description as filed, in particular on page 14, lines 17 to 30, the scheme on page 21 and the common general knowledge as represented by the documents (5) and (6), the Board has no serious reason to cast doubt on the fact that the claimed imidazoles, di- or trisubstituted at their C-atoms, can be prepared.

4.2 Therefore, the requirement of Article 83 EPC is met.

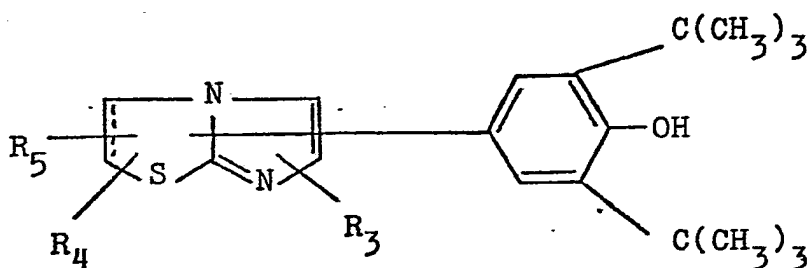
5. *Article 54 EPC*

After examination of the cited prior art documents, the Board has reached the conclusion that the subject matter of Claims 1 and 6 to 8 is novel since none of the documents (1) to (3) disclose 5-pyrimidinol substituted imidazole. Since this was not disputed, it is not necessary to give detailed reasons for this finding.

6. *Inventive step - Article 56 EPC*

6.1 The claimed invention relates to 2-imidazolyl-5-hydroxy-1,3-pyrimidines of formula I (cf. point II above) having activity as inhibitors of 5-lipoxygenase and / or cyclooxygenase providing, in particular, treatment of inflammatory conditions (cf. page 1, lines 13 to 14 and 30 to 31 of the application as filed).

6.2 Document (1) discloses 3,5-di-tert-butyl-4-hydroxyphenyl-(2,3-dihydro)imidazo[2,1-b]thiazole compounds of formula:



wherein the sulfur atom of the heterocycle optionally carries one or two oxygen atom(s), R₃, R₄ and R₅ being selected from hydrogen, halogen, C₁ to C₇ alkyl, hydroxy C₁ to C₇ alkyl, amino C₁ to C₇ alkyl, aryl, C₁ to C₇ alkoxy-substituted aryl, C₁ to C₇ alkanoyl, C₁ to C₇

alkylthio, C₁ to C₇ alkoxy, aryl-substituted C₁ to C₇ alkyl, cyano and thiocyanato, having a lipoxygenase suppressing activity (cf. pages 1 and 2; page 3, lines 18 to 19) and useful as anti-inflammatory agents (cf. page 4, lines 16 to 18).

- 6.3 The Board considers, in agreement with the Examining Division and the Appellant, that the closest state of the art is represented by the disclosure of document (1). Indeed, this document aims at the same objective and has the most relevant technical features in common with the claimed subject matter.
- 6.4 In the light of this closest state of the art, the technical problem to be solved may be seen, as held by the Examining Division and submitted by the Appellant, in the provision of further compounds having the said activity (cf. point 6.2 above).
- 6.5 The Examining Division relying upon the decisions T 939/92 (OJ EPO 1996, 309), in particular point 2.4.2 of the reasons, and T 964/92 held that, although the person skilled in the art would not have arrived at the claimed invention in view of the structural differences between the claimed compounds and document (1) and, consequently, an inventive concept underlay the present claims, it had not been made credible that all members of the claimed group of compounds solved the technical problem (cf. point 6.4 above). Reference was made, in particular, to the compounds of formula (I) where R₃ was a phenyl radical substituted by three nitro groups or where R₃ and R₄ were a phenyl radical.

The Appellant argued that the present case differed from those having led to the decisions T 939/92 and

T 964/92 (loc.cit), given that in those previous cases the issue was the equivalence and sufficient disclosure of substituents in systems showing a high degree of similarity in their chemical structure while in the present one, the gist of the invention was the new heterocyclic imidazole-pyrimidine ring system and the substituents did not contribute more to the activity than the substituents R₃, R₄ and R₅ of document (1) (cf. point 6.2 above).

The Board concurs with the Appellant's submissions that the situations which prevailed in both previous cases (T 939/92 and T 964/92) are different from the present one.

In T 939/92, the sole difference between the compounds of the prior art and the claimed compounds was the replacement of one substituent attached to an identical sulfonamide substituted triazole ring.

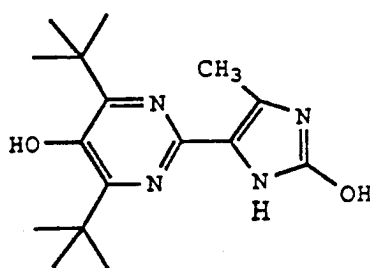
In T 964/92, the sole difference between the compounds of the prior art and the claimed compounds was the replacement of one substituent attached to an identical 2-nitratomethyl-benzodioxane ring.

In both case, the substituents attached to the heterocycle ring were the sole distinguishing features and those Boards found it justified to question whether or not all the defined substituents led to compounds which could solve the technical problem.

By contrast, in the present case, the fundamental difference between the compounds of document (1) and the claimed compounds lies on the ring system (4-phenol attached to **any** position of a (2,3-dihydro)imidazo[2,1-

b) thiazole ring versus 5-pyrimidinol attached to **any** C-atom of an imidazole ring, respectively). Therefore, the question is whether the new **ring system** credibly solves the above defined problem (cf. point 6.4 above).

The present application discloses, as an example, the activity of 4,6-bis(1,1-dimethylethyl)-2-(2-hydroxy-5-methyl-1H-imidazol-4-yl)-5-pyrimidinol of formula



on 5-lipoxygenase and cyclooxygenase of ARBL/ARBC whole cell.

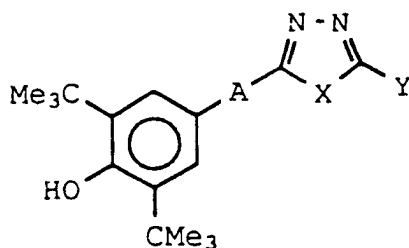
Since it is known from the closely related prior art, i.e. document (1), that a 3,5-ter-butyl 4-hydroxyphenyl group attached to **any** position of a (2,3-dihydro)imidazo[2,1-b] thiazole ring itself substituted preserves globally the biological activity, in the absence of any proof to the contrary the Board has no reason to doubt that in the claimed invention the biological activity is preserved when the pyrimidinol ring is attached to any position of the imidazole ring. In that case, contrary to the situations which prevailed in T 939/92 and T 964/92, the nature of the substituents becomes secondary in view of the technical contribution to the art constituted by the provision of a new ring system and the inventive step is not to be assessed vis-à-vis the nature of those substituents. Therefore, the Board holds that, in the present case,

an objection against the nature of the substituents attached to the imidazole ring is not justified. For the sake of argument, the Board observes, furthermore, that those substituents are similar to the substituents present on the (2,3-dihydro)imidazo[2,1-b]thiazole ring disclosed in document (1) and that there is no serious reason to believe in that case that the biological activity of the ring system is affected by the group of listed substituents. Therefore, the Board comes to the conclusion that the technical problem is credibly solved for all the compounds encompassed by Claim 1.

6.6 It remains to be decided whether or not the compounds of Claim 1 are obvious in view of the cited prior art.

The compounds according to the claimed invention can be distinguished from document (1) in that the two heterocycles attached to each other are different (pyrimidinol versus phenol and imidazole versus (2,3-dihydro)imidazo[2,1-b]thiazole) (cf. point 6.2 above).

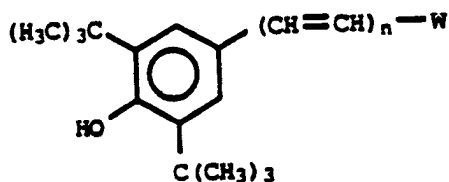
Document (2) discloses antiinflammatory agents having activity as inhibitors of 5-lipoxygenase, cyclooxygenase or both (cf. page 5, lines 46 to 49) of formula:



wherein X is O or S.

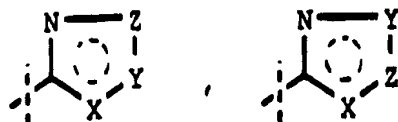
(cf. page 2, lines 1 to 14).

Document (3) discloses antiinflammatory agents having activity as inhibitors of 5-lipoxygenase, cyclooxygenase or both (page 2, lines 4 to 9) of formula:



I

wherein W is



X being N, NR₁, O or S,

Z being O, S, NR₁ or N

(cf. page 3, lines 4 to 23).

The Board observes that starting from document (1), the person skilled in the art would have found no relevant information in the disclosures of documents (2) and (3) since none of them teach the replacement of a phenol ring by a pyrimidinol ring and a (2,3-dihydro)imidazo[2,1-b]thiazole ring by a imidazole

ring. This finding was not disputed by the Examining Division.

It follows from the above that the subject-matter of Claim 1 is not rendered obvious by the cited prior art. The same applies to the dependent Claims 2 to 5 relating to specific embodiments of said independent Claim 1.

Independent Claims 6, 7 and 8 are based on the same inventive concept and derive their patentability on the same basis as does Claim 1.

Auxiliary requests

7. It follows from the above that the Appellant's auxiliary requests need not be examined.

8. *Procedural matters*

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.

9. *Remittal to the first instance - Article 111(1) EPC*

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 description has still to be put into conformity with the Claims of the present main request, **in particular the correction on page 9, line 25 of the figure "1" by the figure "6"** (cf. point 2 above). 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 exercises its discretion under Article 111(1) EPC to remit the case to the first instance in order for the description to be adapted to the allowable claimed subject-matter according to the main request.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the first instance with the order to grant a patent with the Claims 1 to 9 submitted as main request on 16 January 1998 and a description to be adapted, in particular the correction on page 9, line 25 of the Figure "1" by the Figure "6".

The Registrar:

The Chairman:

N. Maslin

P. P. Bracke