BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | **BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE** | **CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS**

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D E C I S I O N
of 6 June 1994

Case Number: T 0852/91 - 3.3.1

Application Number: 86308053.7

Publication Number: 0227241

IPC: C07D 309/08

Language of the proceedings: EN

Title of invention:
Medicinal indole and indazole keto sulphone derivatives

Applicant:
ICI AMERICAS INC.

Opponent:
-

Headword:
Leukotriene antagonist/ICI AMERICAS

Relevant legal norms:
EPC Art. 56

Keyword:
"Inventive step (yes)"
"Structural similarity of chemical compounds"
"Existence of common general knowledge regarding equivalency - contested"

Decisions cited:
-

Catchword:

To deny inventive step for novel chemical compunds because of their "structural similarity" to known chemical compounds would be justified, if the skilled person knew, be it from common general knowledge, or from some specific disclosure, that the existing structural differences of the chemical compunds concerned were so small that they would have no essential bearing on those properties which are important for solving the technical problem underlying the invention (No. 8.2)

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0852/91 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 6 June 1994

Appellant: ICI AMERICAS INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office dated 27 June 1991 refusing European patent application No. 86 308 053.7 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. Jahn
Members: P. Krasa
J.A. Stephens-Ofner

Summary of Facts and Submissions

I. European patent application No. 86 308 053.7 (publication No. 227 241) was filed on 16 October 1986 claiming two British priorities of 17 October 1985 and 15 April 1986.

II. By a decision dated 27 June 1991, which was based on Claims 1 to 9, 12, 13, 15, and 16 as originally filed and on Claims 10, 11 and 14 as filed with letter of 23 May 1989, the Examining Division refused the application on the grounds that the subject-matter of Claim 1 was not inventive over document

(A) EP-A-0 179 619 (published 30 April 1986)

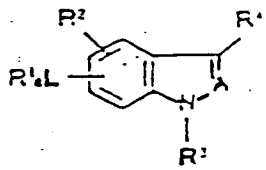
as far as such subject-matter did not enjoy the claimed priority right.

III. An appeal was lodged against this decision on 24 August 1991 with payment of the appropriate fee. In his Statements of Grounds of Appeal, filed 13 September 1991, the Appellant contended that the subject-matter of the above Claim 1 was inventive. He also submitted (as an auxiliary request) a second set of Claims 1 to 11 for all designated states except AT, GR and ES and one claim for AT, GR and ES. The Appellant requested that the decision under appeal be set aside and the application be remitted to the Examining Division for further consideration either with the Claims 1 to 16 as rejected by the Examining Division (main request) or, alternatively, with the claims according to the auxiliary request. The Appellant further requested that oral proceedings be held, in case the Board intended to refuse the appeal.

IV. In a communication from the Board pursuant to Article 110(2) EPC, dated 14 March 1994, a number of objections were raised regarding the language of the claims of the main request. In reply the Appellant submitted on 16 May 1994 a new set of Claims 1 to 16 for all designated states except AT, GR and ES, and one Claim for AT, GR and ES.

Independent Claim 1 of the amended set of claims for the Contracting States other than AT, GR, and ES according to the main request reads:

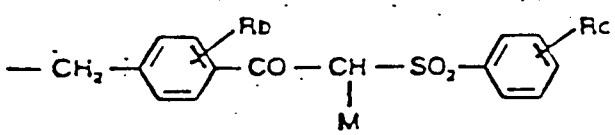
"A compound of formula I



(I)

wherein
=A- is a group of formula =C(Ra)- or =N- in which Ra is hydrogen or (1-4C)alkyl;
the group R^1.L is an amidic radical of formula R^1.W.CO.NH-, R^1.W.CS.NH- or R^1.NH.CO, in which R^1 is selected from (a) (2-10)alkyl optionally containing 1 or more fluorine substituents; (b) phenyl-(1-6C)alkyl in which the (1-6C)alkyl moiety may optionally bear a fluoro or (1-4C)alkoxy substituent and in which the phenyl moiety may optionally bear a substituent selected from halogeno, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl; and (c) (3-8C)cycloalkyl, (3-8C)cycloalkenyl, (3-8C)cycloalkyl-(1-6C)alkyl or (3-8C)cycloalkenyl-(1-6C)alkyl, the cyclic moiety of any of which optionally may bear 1 or 2 (1-4C)alkyl substituents, and

W is oxy, thio, imino or a direct link to R^1;
R^2 is hydrogen, halogeno, (1-4C)alkyl or (1-4C)alkoxy;
one of R^3 and R^4 is a radical of formula II:



(II)

wherein
Rb is hydrogen, (1-4C)alkyl or (1-4C)alkoxy;
Rc is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, trifluoromethyl or halogeno; and
M is hydrogen, cyano, (1-4C)alkoxycarbonyl, carbamoyl, N-phenylcarbamoyl, N-p-tolylcarbamoyl, N-p-chlorophenylcarbamoyl, N-o-tolylcarbamoyl, N-p-anisylcarbamoyl, N-(1-4C)alkylcarbamoyl, N,N-di[(1-4C)alkyl]carbamoyl or (1-6C)alkanoyl;
and the other of R^3 and R^4 is hydrogen, halogeno (provided that R^3 may not be halogeno), (3-8C)cycloalkyl, (3-8C)cycloalkyl-(1-4C)alkyl, or a hydrocarbon radical of 1 to 10 carbon atoms selected from alkyl, alkenyl, alkynyl, alkadienyl, alkadiynyl, said hydrocarbon radical additionally optionally bearing a
substituent P selected from cyano, carboxy, 1H-tetrazol-5-yl, (1-4C)alkoxy, (1-4C)alkoxycarbonyl, carbamoyl of formula CONRdRe, ureido of formula NRfCONRdRe, carbamoyloxy of formula OCONRdRe, a carbamate of formula NRfCOORg, acylamino of formula NRfCORg, acyloxy of formula OCORg, and an optionally oxidized thio group of formula $S(O)_nRg$ in which for
Rd, Re and Rf (1) Rd is selected from hydrogen, (1-6C)alkyl, and phenyl, the phenyl moiety of which may optionally bear 1 or 2 substituents selected from halogeno, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl; and Re and Rf are independently chosen from hydrogen and

(1-6C)alkyl; or (2) Rd and Re together with the adjacent nitrogen form a pyrrole, pyrrolidine, piperidine, morpholine, piperazine or N-(1-6C)alkylpiperazine ring; and Rf is hydrogen or (1-6C)alkyl;
Rg is selected from (1-4C)alkyl, and phenyl, the phenyl moiety of which may optionally bear 1 or 2 substituents selected from halogeno, (1-4C)alkyl, (1-4C)alkoxy and trifluoromethyl; and
n is the integer 0, 1 or 2;
or a pharmaceutically acceptable salt thereof."

The Appellant requested grant of a patent on the basis of these claims.

Reasons for the Decision

1. The appeal is admissible.

2. There are no objections under Article 123(2) EPC to the present version of the claims. In particular, Claim 1 is based on Claim 1 as originally filed and page 8, lines 20 to 23 (definition of M); Claim 2 is based on Claim 2 as originally filed and page 5, lines 25 to 26 (definition of Rd and Re); Claim 14 (and the claim for the designated states AT, GR, and ES) is based on Claim 14 (respectively the claim for the designated states AT, GR, and ES) as originally filed and page 11, lines 25 to 28; Claims 3 to 13, 15, and 16 are, apart from minor editorial amendments and terminological clarifications, identical with the respective claims as originally filed.

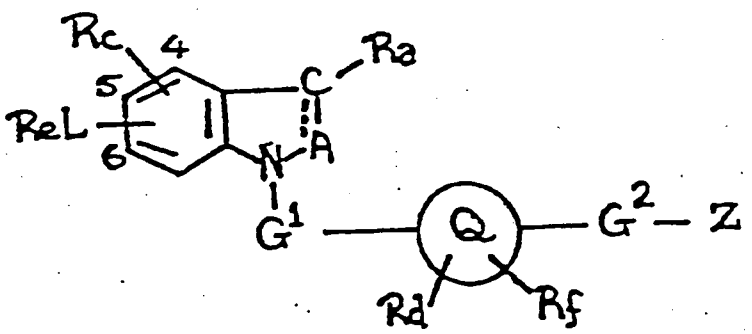
3. The application in suit relates to substituted indoles and indazoles of formula I (see above No. IV) and their pharmaceutically acceptable salts, which compounds and salts are useful in antagonising the action of

leukotrienes (see the application in suit, page 1, line 1 to page 2, line 32, in combination with page 17, lines 3 to 4, and, e.g. page 20, lines 7 to 10).

The present Claim 1 encompasses compounds not enjoying the claimed priority right. In particular compounds of formula I are concerned wherein

R^1	is phenyl-(1-6C)alkyl with one fluoro substituent in the alkyl moiety; or
Rc	is (1-4C)alkoxy or trifluoromethyl; or
one R^3 or R^4	is (1-10) alkynyl, alkadiynyl, or alkenynyl;
P	is -NRfCORg or OCORg; or
Rd and Re	are together with the adjacent nitrogen pyrrole or pyrrolidine.

Document (A) qualifies as state of the art in respect to these compounds and the Board takes this citation as starting point for evaluating inventive step. It discloses indoles and indazoles of the formula



wherein

Q	is a direkt link to G^1, or is oxy, thio, m-phenylene, p-phenylene or heteroarylene;
G^1	is (1-8C)alkylene or (2-6C)alkenylene;
G^2	is methylene, vinylene or a direct link to Z; and

Z is an acidic group selected from carboxy, an acylsulphonamide residue of the formula $-CO.NH.SO_nRg$ and a [substituted] tetrazolyl residue; and

Rg is, *inter alia*, aryl; e.g. phenyl, optionally substituted by F, Cl, CH_3, NO_2 or amino;

n is the integer 1 or 2

(page 2, line 29 to page 4, line 2, in combination with page 9, lines 26 to 28, and with the formula I of the formulae sheet).
The meaning of the other symbols is of no importance for the present case.

All the compounds disclosed in document (A) have leukotriene antagonising properties (page 1, lines 3 to 9, page 18, lines 31 to 32, and page 21, lines 30 to 33).

4. Therefore, in the light of this closest prior art, the technical problem underlying the application in suit is to provide further indoles and indazoles with leukotriene antagonising properties.

5. According to the application in suit, this technical problem is essentially solved by the compounds of formula I as defined in the present Claim 1. In view of the statement that these compounds demonstrated a statistically significant activity as LTC_4, LTD_4 and/or LTE_4 antagonists in particular tests at a concentration of about 10^{-5} M or less (page 20, lines 7 to 10), and having regard to the fact that these statements remained unchallenged by the Examining Division, the Board is satisfied that the above defined technical problem is actually solved.

6. After examination of the prior art cited in the search report, the Board finds that the subject-matter of the present claims is novel. Since novelty was not in dispute, it is not necessary to give detailed reasons for this finding.

7. It still remains to be decided whether the claimed subject-matter involves an inventive step.

7.1 The group of compounds generically disclosed in document (A) encompasses a sub-group of compounds where the assembly of the symbols $-G^1-Q-G^2-Z$ designates the residue

$$-CH_2-(p-C_6H_4)-Z$$

wherein the C_6H_4 group is optionally substituted. A number of examples is representative for this sub-group (see e.g. examples 34 to 43, pages 37 to 38, in combination with formula 5 on page 113 for Z = COOH; examples 67, 68, 150, and 151, pages 41, 42, 57, and 58, in combination with formula 17 on page 116 for Z = tetrazolyl; and examples 255 to 264, pages 91 to 95 for Z = $-CONHSO_2Rg$).

The compounds of present Claim 1 differ from those of this sub-group of citation (A) mainly by replacement of the group Z by the group

$$-COCH(M)SO_2-C_6H_4-Rc.$$

7.2 The Examining Division stated "From document (A) it is known that indole or indazole derivatives bearing in the heterocyclic ring a benzyl group which is substituted by an acidic group, which is selected from different types of acidic residues, antagonise leukotrienes." - see page 4, 3rd paragraph of the grounds for the decision - and held that all the groups Z being acidic ones, a

"... skilled person would have expected that compounds of the same basic structure which differ only in the type of the acidic substituent will also antagonise leukotrienes ..." (grounds for the decision, page 4, first sentence of the last paragraph). The Examining Division concluded that the present compounds were structurally closely related to those of document (A) and, thus, in the absence of any showing of an unexpected effect, obvious over the latter.

8. The Board cannot accept this conclusion, nor the argument that gave rise to it.

8.1 First of all, the actual disclosure of document (A) in respect to the residue Z has to be established. The relevant sentence bridges pages 2 and 3 and reads: "Z is an acidic group selected from carboxy, an acylsulphonamide residue of the formula $-CONHSO_nRg$ and a tetrazolyl residue ...". In the Board's judgement, this sentence specifies three particular (generic) alternatives for the meaning of the symbol Z. In the compounds concerned, Z necessarily must be one of these three possibilities and there is no indication in document (A) that the leukotriene antagonising properties would be maintained when those specified residues were replaced by any other "acidic" group. While the term "acidic" designates a property, which all the three alternatives of Z have in common, this sentence cannot be construed as teaching that any other conceivable "acidic" group, could be used as an equivalent for Z in respect to the leukotriene antagonising activity of the underlying compounds.

8.2 The Examining Division further relied on a structural similarity of the arylsulphonamide residue $-CONHSO_nRg$ of document (A) and the present ketosulphonyl group $-COCH(M)SO_2-C_6H_4-Rc$.

To deny inventive step for novel chemical compounds because of their "structural similarity" to known chemical compounds amounts to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means for solving the technical problem underlying the application in question. Such an expectation would be justified, if the skilled person knew, be it from common general knowledge or from some specific disclosure, that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on those properties, which are important for solving the said technical problem and could be disregarded.

8.3 The Examining Division did not cite any particular document in support of their argument that the $-COCH(M)SO_2-C_6H_4-Rc$ group of the application in suit would act as an equivalent to the $-CONHSO_nRg$ group of document (A) in respect to the leukotriene antagonising properties of the respective compounds, but obviously relied on the supposed existence of some common general knowledge. This approach is contrary to the principle that in proceedings before the EPO objections against patentability have to be based on verifiable facts.

8.4 The Appellant submitted that there is nothing in the state of the art from which a skilled person would have deduced that the substitution of a group Z in the compounds of document (A) by a ketosulphonic group would still result in leukotriene antagonists and thereby contested the existence of such a common general knowledge, which existence was neither rendered plausible by the Examining Division nor is known to the Board. In such a situation and taking into account that, according to the Board's own knowledge, even minute structural differences may have a strong impact on the

biological or pharmacological properties of chemical compounds, the Board finds that inventive step cannot be denied for the chemical compounds of present Claim 1 merely on the basis of an alleged structural similarity with the chemical compounds known from document (A).

9. The Examining Division acknowledged in their communication of 16 January 1989 that the ketosulphonic group as a structural feature of the present compounds was not rendered obvious by documents (B) or (C) (page 2, lines 14 to 24). The Board has no reason to deviate from such finding.

10. For the above reasons, the Board finds that the subject-matter of Claim 1 for all the designated states other than AT, GR, and ES involves an inventive step within the meaning of Article 56 EPC. The subject-matter of Claims 14 to 16 for all the designated states other than AT, GR, and ES concerning methods of making the compounds of Claim 1, pharmaceutical compositions comprising them and their use for the manufacture of a medicament for use in antagonising one or more of the actions of one or more types of leukotrienes in a living animal and the claim for AT, GR, and ES which relates to processes for producing a compound of formula I, define the same invention as Claim 1 in different patent categories. Dependent Claims 2 to 13 for all the designated states other than AT, GR, and ES, relate to specific embodiments of this invention. Therefore, these claims are likewise allowable.

However, the description is not yet adapted to the present claims. Thus, not all requirements of the EPC are met by the present application documents. The Board therefore uses its power under Article 111(1) EPC and remits the case to the Examining Division for proper adaptation of the description.

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 with the order to grant a patent with the two sets of claims submitted on 16 May 1994, after appropriate adaptation of the description.

The Registrar: The Chairman:

E. Görgmaier A. Jahn