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D E C I S I O N
of 17 March 2005

Case Number: W 0015/04 - 3.3.2

Application Number: PCT/EP 03/06739

Publication Number: WO 2004/004725 A2

IPC: A61K 31/46

Language of the proceedings: EN

Title of invention:
New pharmaceutical compositions based on novel anticholinergics and p38 Kinase inhibitors

Applicant:
Boehringer Ingelheim Pharma GmbH & Co. KG

Opponent:
-

Headword:
Anticholinergic and p38 kinase inhibitor composition/BOEHRINGER INGELHEIM

Relevant legal provisions:
EPC Art. 154(3)
PCT Art. 17(3)(a)
PCT R. 40.1, 40.2, 13.1

Keyword:
"General concept not inventive - mere statement of synergism, combination obvious"

Decisions cited:
W 0045/92, W 0003/94, W 0006/94

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: W 0015/04 - 3.3.2

International Application No. PCT/EP 03/06739

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 17 March 2005

Applicant: Boehringer Ingelheim Pharma GmbH & Co. KG
Binger Strasse 173
D-55216 Ingelheim am Rheim (DE)

Representative: -

Decision under appeal: **Protest according to Rule 40.2(c) of the Patent Cooperation Treaty made by the applicants against the invitation (payment of additional fees) of the European Patent Office (International Searching Authority) dated 19 January 2004.**

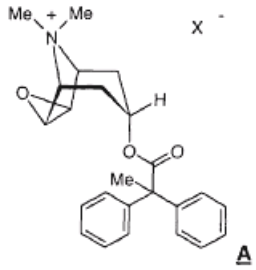
Composition of the Board:

Chairman: U. Oswald
Members: H. Kellner
B. Günzel

Summary of Facts and Submissions

I. The applicant filed an international patent application, No. PCT/EP 03/06739, comprising a set of 28 claims, claim 1 of which reads as follows:

"1. Pharmaceutical compositions characterised in that they contain one or more anticholinergics of formula **A**



A

wherein

X^- denotes an anion (counter-ion), preferably an anion selected from the group consisting of chloride, bromide, iodide, sulphate, phosphate, methansulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate

combined with one or more p38 kinase inhibitors (**B**), optionally in the form of the enantiomers, mixtures of the enantiomers or in the form of the racemates thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutical acceptable excipient."

II. In its communication dated 19 January 2004, the European Patent Office, acting as an International Searching Authority (ISA), invited the applicant pursuant to Article 17(3)(a) and Rule 40.1 PCT to pay four additional search fees.

The ISA found that the subject-matter of the present application was concerned with binary pharmaceutical compositions, comprising a first component of formula A, which was an anticholinergic agent and a second component, which was a p38 kinase inhibitor of formulae B1 to B7. The compositions were useful in the treatment of chronic obstructive pulmonary disease (COPD) and other diseases of the upper or lower respiratory tract, like allergic and non—allergic rhinitis.

In this respect the ISA cited page 1, lines 10 to 21 of the application as filed, where the applicant stated that the claimed compositions exhibited an unexpectedly beneficial effect, particularly a synergistic effect, and that these compositions could be used in lower doses than was the case when the individual compounds were used in monotherapy in the usual way.

Since there was no other statement of unexpected or advantageous properties of the combinations claimed and since even the statement cited was experimentally unsupported, the ISA concluded that there was a lack of "any factual indication" of such effects in the whole application.

Taking into account that document WO-A-0232899 (1) disclosed compounds of formula A especially being active against COPD and asthma, it was found therefore to constitute the closest prior art document.

The technical problem which the application set out to solve versus the closest prior art could therefore be

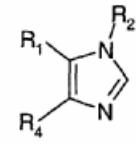
formulated as "how to provide an alternative composition for the treatment of the aforementioned diseases" and the common concept linking the different compositions A + B1 to B7 as claimed subject-matter for solving the problem was that a combination of anticholinergics and p38 kinase inhibitors treated the diseases mentioned.

Since WO-A-9901130 (2) disclosed that the compounds of Formula B1 were p38 kinase inhibitors and since they were claimed for the treatment of asthma and COPD (there called chronic pulmonary inflammatory disease) and since additionally various other documents taught or at the very least suggested that p38 kinase inhibitors were active in the treatment of COPD and other diseases of the respiratory tract and since finally WO-A-0190074 (6) explicitly suggested combining p38 kinase inhibitors with anticholinergic agents for the treatment of asthma, it was concluded that the common concept linking the present alleged inventions was obvious to the person skilled in the art.

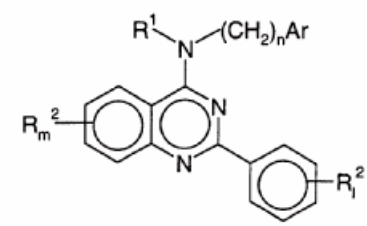
Additionally, there was no other single inventive concept which could link them, since for example the different components B did not share any common structural feature. Thus, the present invention lacked unity in the sense of Rule 13.1 PCT.

The following groups of inventions were identified by taking account of the different structural features of the compositions of formulae B1 to B7:

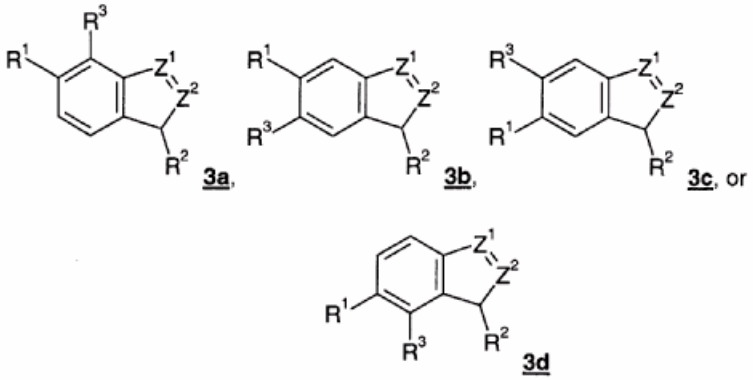
Group 1: claims: 1–6 (in part), 7, 15–28 (in part)
Pharmaceutical compositions comprising an anticholinergic of formula A and a p38 kinase inhibitor B of formula 1



Group 2: claims: 1–6 (in part), 8, 15–28 (in part)
Pharmaceutical compositions comprising an anticholinergic of formula A and a p38 kinase inhibitor B of formula 2

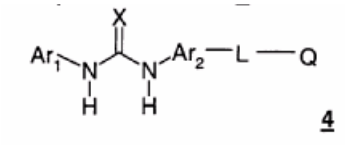


Group 3: claims: 1–6 (in part), 9, 15–28 (in part)
Pharmaceutical compositions comprising an anticholinergic of formula A and a p38 kinase inhibitor B of formulae 3a–3d



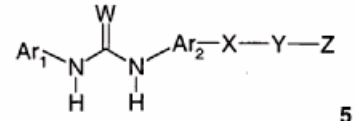
3a, 3b, 3c, or 3d

Group 4: claims: 1—6 (in part), 10, 15—28 (in part)
Pharmaceutical compositions comprising an anticholinergic of formula A and a p38 kinase inhibitor B of formula 4



4

Group 5: claims: 1—6 (in part), 11, 12, 13, 14, 15—28 (in part)
Pharmaceutical compositions comprising an anticholinergic of formula A and a p38 kinase inhibitor B of formulae 5, 5a, 6 and 7



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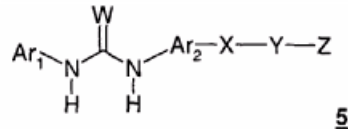
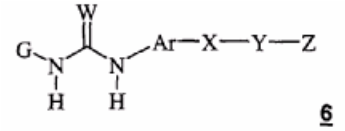


5a



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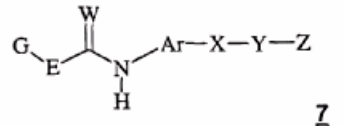

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III. With its reply, dated 29 January 2004, the applicant paid one additional search fee under protest pursuant to Rule 40.2(c) PCT and requested that alleged inventions group 1 and 5 be searched.

In support of the protest, the applicant argued that the ISA had already acknowledged the common concept of a combination of anticholinergics of formula A and p38 kinase inhibitors B for the treatment of respiratory diseases and therefore unity a priori was given.

With respect to unity a posteriori, the applicant submitted that (1) did not mention "p38 MAP kinase inhibitors" and none of the other cited documents disclosed compounds of general formula A.

Therefore, and because the application in hand at least indicated the existence of unexpected or advantageous properties of the claimed subject-matter, the cited state of the art could not lead without reasonable doubt to the finding that the invention in question was not inventive.

With reference to decision W 45/92 of 15 October 1993, in such a case non-unity should not be declared.

IV. In a prior review pursuant to Rule 40.2(e) PCT, dated 6 April 2004, the review panel of the ISA found the invitation to pay additional fees to be justified and invited the applicant to pay the protest fee.

In summary, the review panel considered that, in the light of document (6), the concept of combining anticholinergic agents with p38 kinase inhibitors was known and therefore the concept of selecting particular anticholinergic agents of formula A and combining them with p38 kinase inhibitors B without any resulting new/surprising technical effect could not act as a

unifying inventive concept linking invention subjects 1 to 5.

The application merely stated on page 1 that there was a synergistic effect without any substantiation and the fact that each of the groups of p38 kinase inhibitors defined in the claimed subjects 1 to 5 had very different structures, made it unlikely that a synergistic effect could be shown to be valid across the full scope of claim 1.

Since the evaluation of unity had to be carried out on the application documents as originally filed, and since the application was silent about comparative tests showing the existence of a surprising technical effect, the review panel was of the opinion that the ISA was right in its conclusions.

V. With a letter of 14 April 2004, the applicant paid the protest fee according to Rule 40.2(e) PCT.

Reasons for the Decision

1. Under Article 154(3) EPC, the boards of appeal are responsible for deciding on the protest made by the applicant.

2. The protest complies with the requirements of Rule 40.2(c) PCT and is therefore admissible.

3. General requirements for protest proceedings pursuant to Rule 40.2 PCT are as follows:

3.1 Pursuant to Rule 40.2 PCT, the board must examine the protest and, to the extent that it finds the protest justified, order the full or partial reimbursement to the applicant of additional fees, as far as they were paid in fact and under protest.

3.2 According to the established practice of the boards of appeal, the examination in protest proceedings has to be carried out in the light of the reasons given by the ISA in its invitation to pay additional fees under Rule 40.2 PCT and the applicant's submissions in support of the protest.

4. In the present case, the ISA's invitation to pay additional fees is based on the findings that document (1) disclosed compounds of formula A especially being active against COPD and asthma and that it therefore constituted the closest prior art document. These conclusions were not contested by the applicant in its statement under Rule 40.2(c) PCT.

The board sees no reason to differ.

4.1 The single inventive concept linking a group of inventions is to be derived from the common features of the respective claims together with the outcome or results associated with this subject-matter.

Thus, the concept of combining anticholinergic agents of formula A with p38 kinase inhibitors of formulae B1 to B7 for treatment of COPD and other diseases of the upper or lower respiratory tract, such as allergic and non—allergic rhinitis (see page 134, lines 1 to 15, and

page 1, lines 10 to 21, of the current application), is to be seen as this link.

4.2 None of the cited documents discloses a combination of anticholinergic agents of formula A and p38 kinase inhibitors B. Thus the concept set out under point 4.1 is new.

But Rule 13.1 PCT also stipulates that the single general concept must be inventive.

4.3 From the description of the current application (see page 1, lines 14 to 21) it seems that the problem to be solved lay in providing a therapeutic formulation for the treatment of diseases of the upper or lower respiratory tract, being superior to known formulations because of a synergistic effect that gives the possibility of administering lower doses than is the case when the individual compounds are used in monotherapy in the usual way. These doses especially should be effective for treating inflammatory or obstructive diseases of the respiratory tract, particularly asthma, chronic obstructive pulmonary diseases (COPD) and/or pulmonary hypertension (see application as originally filed, page 134, lines 1 to 5).

However, in the absence of any comparative experiment in the application as originally filed, particularly with respect to the closest state of the art, there is no factual indication that the synergistic effect and the possibility of administering lower doses do in fact exist.

Moreover, it is common general knowledge that synergism as alleged in the present case, where it occurs, is normally observed only with respect to combinations of individual compounds. While it may be expected that the synergistic effect will still be obtained if minor variations of these individual compounds are made, such an expectation is not reasonable in the case of more far reaching (significant) variations. Accordingly, it is even less credible that such a synergistic effect will be retained in the case that a plurality of fundamentally different structures are considered. This latter case corresponds to the five highly heterogeneous structure groups for the p38 kinase inhibitors according to the definition of groups 1 to 5 by the ISA from the present claims. Thus, it is not credible that a synergistic effect could ever be shown to be valid across the full scope of claim 1.

Therefore, the definition of the problem, implied in the application as filed and depending on the existence of the alleged synergistic effect, cannot be acknowledged. Under the given circumstances, the problem must be defined as providing just another medicament for the treatment of respiratory diseases such as COPD or asthma.

This problem may plausibly be solved by a pharmaceutical combination of anticholinergic agents of formula A and p38 kinase inhibitors B.

Since (1) indicates the possibility of combining anticholinergic agents of formula A with other pharmaceutically active substances (see page 25, lines 12 to 16), especially for treatment of asthma and

COPD (see page 25, lines 6 to 8) and since (6) explicitly suggests combining p38 kinase inhibitors with anticholinergic agents (see page 28, lines 16 to 31) for the treatment of asthma, it was obvious for the person skilled in the art to combine anticholinergic agents of formula A with p38 kinase inhibitors for treating said diseases. The compounds of formula B1, for instance, are known as p38 kinase inhibitors from (2), page 40, lines 3 to 7, together with page 5, lines 31 to 33, and page 6, lines 6 to 8.

Thus, the single general concept linking the subject-matter of claims 7 to 14 is not inventive. Additionally, it cannot contribute to the inventiveness of the subject-matter of claim 1 as originally filed, since the technical features contained in the single general concept and in claim 1 are identical.

5. The main argument submitted by the appellant was that experimental support for the presence of unexpected or advantageous properties could be submitted after the application date and therefore substantive examination of the claimed subject-matter for inventive step, being part and parcel of the examination of unity in the present case, was not within the competence of the search authority.

This argument cannot lead to success in the present case because the decision on the applicant's claim for refund of the additional search fee paid and, **in this context**, on the issue of unity has to be taken on the basis of the case as it stands when the decision is taken. Based on this, the existence of synergism as a beneficial effect over all the five groups of

inventions defined by the ISA was not credible and it was moreover not credible that a synergistic effect could ever be shown to be valid across the full scope of claim 1.

6. As regards the additional search fee paid for the search of the invention of group 5, for the reasons given under point 4 of this decision, the board finds the applicant's protest not to be justified, so that the protest has to be dismissed.

Order

For these reasons it is decided that:

The protest is dismissed.

The Registrar: The Chairman:

A. Townend U. Oswald