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D E C I S I O N
of 30 September 2003

Case Number: T 0133/01 - 3.3.1

Application Number: 96307616.1

Publication Number: 0771800

IPC: C07D 491/056

Language of the proceedings: EN

Title of invention:
Dioxino derivatives and their use as dopamine agonists

Applicant:
Wyeth

Opponent:
-

Headword:
Dopamine agonists/WYETH

Relevant legal provisions:
EPC Art. 56, 123(2)

Keyword:
"Inventive step (no) - enabling disclosure of closest prior art - unfair comparative tests - alternative - arbitrary selection"

Decisions cited:
T 0020/81, T 0181/82, T 0206/03, T 0026/85

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0133/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 30 September 2003

Appellant: Wyeth
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 3 April 2000 refusing European application No. 96307616.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

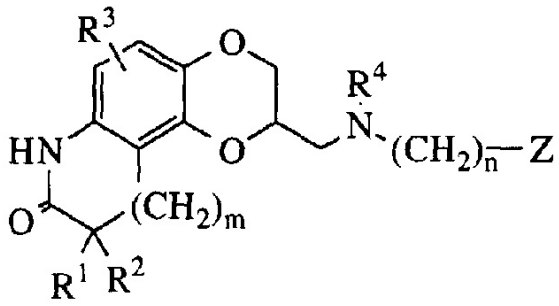
Chairman: A. J. Nuss
Members: R. Freimuth
S. U. Hoffmann

Summary of Facts and Submissions

I. The appeal lodged on 11 October 2000 lies from the decision of the Examining Division posted on 3 August 2000 refusing European patent application No. 96 307 616.1 (European publication No. 771 800).

II. The decision of the Examining Division was based on claims 1 to 44 of the application as filed. Claim 1 and dependent claim 4 read as follows:

"1. A compound of formula I



I

wherein

R^1 and R^2 are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, phenyl or benzyl; or R^1 and R^2, taken together, are benzylidene optionally substituted with R^3 as defined below or alkylidene of up to 6 carbon atoms, or R^1 and R^2, taken together with the carbon to which they are attached, form a carbonyl moiety or a cycloalkyl group having three to 6 carbon atoms;

R^3 is hydrogen, hydroxy, halo, trifluoromethyl, trifluoromethoxy, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, arylalkoxy of 7 to 12 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6

carbon atoms, alkanamido of 2 to 6 carbon atoms or alkanesulfonamido of 1 to 6 carbon atoms;
R^4 is hydrogen or alkyl of 1 to 6 carbon atoms;
m is one of the integers 0, 1 or 2;
n is one of the integers 0, 1, 2, 3, 4, 5, or 6;
Z is hydrogen, hydroxy, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, alkynyl of 2 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, cycloalkyl of 3 to 8 carbon atoms, polycyclic alkyl of 7 to 15 carbon atoms, phenyl optionally substituted with R^3 as defined above, phenoxy optionally substituted with R^3 as defined above, naphthyl optionally substituted with R^3 as defined above or naphthyloxy optionally substituted with R^3 as defined above, heteroaryl or heteroaryloxy, in which the heterocyclic ring of the heteroaryl or heteroaryloxy group is selected from thiophene, furan, pyridine, pyrazine, pyrimidine, indole, indazole, imidazole, chroman, coumarin, carbostyril, quinoline, benzisoxazole, benzoxazole, pyrazole, pyrrole, thiazole, oxazole, or isoxazole and the heterocyclic ring is optionally substituted by R^3 as defined above;
or a pharmaceutically acceptable salt thereof."

"4. The compound of Claim 1, which is 2-(benzylamino-methyl)-2,3,8,9-tetrahydro-7H-1,4-dioxino[2,3-e]indol-8-one, which may be an individual enantiomer or a mixture of enantiomers, or a pharmaceutically acceptable salt thereof."

III. The Examining Division found that the subject-matter claimed lacked inventive step and held in particular that the claimed compounds were obvious alternatives of the structurally related compounds known from the documents

(1) WO-A-91/13872 and

(2) J. Med. Chem. 35, 3058 to 3066 (1992).

It would have been only necessary to prove that the compounds really possessed a selective dopamine receptor activity. However, comparative tests with the compound with the highest dopamine receptor affinity described in document (2) were missing. Therefore the claims were too broad to assume that all the possible compounds covered by the claims showed the alleged effect.

IV. At the oral proceedings before the Board held on 30 September 2003 the Appellant (Applicant) submitted fresh auxiliary requests 1 to 4.

Claim 1 according to auxiliary request 1 differed from claim 1 according to the main request in that the meanings alkyl, phenyl, benzyl, benzylidene, alkylidene and cycloalkyl have been deleted for the substituents R^1 and R^2 as well as the meanings arylalkoxy and alkanoyloxy for the substituent R^3, the meaning alkyl for the substituent R^4 and the meaning 2 for the index m. Dependent claim 4 according to auxiliary request 1 was identical to dependent claim 4 of the main request.

Claim 1 according to auxiliary request 2 restricted claim 1 according to auxiliary request 1 further by deleting additionally the meanings alkenyl, alkynyl and alkoxy for the substituent Z. Claim 3 according to auxiliary request 2, apart from being renumbered, was

identical to claim 4 of the main request and auxiliary request 1.

Claim 1 according to auxiliary request 3 differed from claim 1 according to auxiliary request 2 exclusively in deleting the meanings pyrazine, imidazole, pyrazole, pyrrole, thiazole, oxazole and isoxazole from the list of alternative definitions given for the substituent Z. Claim 3 of auxiliary request 3 was identical to claim 3 of auxiliary request 2.

Independent Claim 1 according to auxiliary request 4, apart from its numbering, was identical to claim 3 of auxiliary requests 2 and 3 and to claim 4 of the main request (cf. point II above) and of auxiliary request 1.

V. The Appellant disputed with respect to inventive step that the claimed compounds were encompassed by document (1). For the general formula given therein, this document did not disclose the meaning of the index "m" in the radical $-(CH_2)_m-OR_2$ and, thus, not the meaning "0" which was, however, necessary to arrive at a compound falling within the present claims. The claimed oxindoles were to be considered as a non-obvious selection of structural elements and groups out of document (1). Furthermore, document (1) did not comprise an enabling disclosure for the compounds described therein since the preparation process indicated in that document via intermediate azides did not work in the case of preparing oxindoles. In support thereof the Appellant provided a declaration of Mr Stack on 24 September 2003.

The Appellant submitted furthermore that there were significant physical and chemical differences between the indoles of documents (1) and (2) and the oxindoles claimed. The claimed compounds had a different activity profile, namely a selective dopamine D_2 receptor agonist activity, as evidenced by the comparative test report submitted together with the Statement of Grounds of Appeal on 15 December 2000. The results thereof showed that the replacement of the indole structure by the oxindole structure caused marked improvements in the D_2-receptor affinity and a considerable improvement in the selectivity as evidenced by the ratio of receptor affinities. Therefore the subject-matter claimed was not obvious.

VI. The Appellant requested that the decision under appeal be set aside and the application be granted on the basis of the set of claims as originally filed (main request) or on the basis of the sets of claims according to auxiliary requests 1, 2, 3 or 4 filed during oral proceedings.

VII. At the end of the oral proceedings the decision of the Board was given orally.

Reasons for the Decision

1. The appeal is admissible.

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

Claim 1 of auxiliary request 1 is based on original claim 1. Claim 1 of auxiliary request 2 finds support

in claims 1 and 2 of the application as filed. The additional amendments in claim 1 of auxiliary request 3 are supported by the list for the substituent Z disclosed on page 4, paragraph 1 of the application as filed. Claim 1 of auxiliary request 4 is identical to original claim 4.

For these reasons, the Board concludes that claim 1 according to any request meets the requirements of Article 123(2) EPC.

3. *Novelty*

The Board is also satisfied that the subject-matter as defined in claim 1 according to any request is novel and meets the requirements of Article 54 EPC. To arrive at compounds covered by claim 1 according to the main request or auxiliary requests 1 to 3, a multiple selection of particular structural elements within the generic disclosure of document (1) is necessary and the individual compound of claim 1 according to auxiliary request 4 is nowhere described in the prior art cited. Since novelty has not been challenged by the Examining Division in the decision under appeal, there is no need to go into more detail for that finding.

4. *Inventive step*

The sole issue arising from this appeal consists in deciding whether or not the subject-matter of claim 1 according to the main request or according to the auxiliary requests 1 to 4 involves an inventive step.

4.1 Independent claim 1 of auxiliary request 4 is directed to a preferred embodiment within the ambit of claim 1 according to any preceding request, namely to the identical subject-matter of dependent claims 3 or 4 of the main and auxiliary requests 1 to 3, respectively (cf. point IV above). Thus, the subject-matter claimed in auxiliary request 4 is covered by that of claim 1 of the main and auxiliary requests 1 to 3. In case the embodiment according to auxiliary request 4 lacked inventive step, such a line of requests would mandatorily result in the conclusion that the preceding main and auxiliary requests 1 to 3, which encompasses that obvious embodiment, at least to that extent, cannot involve an inventive step either. For this reason, it is appropriate that auxiliary request 4, in particular the subject-matter of claim 1 thereof, is examined first as to its inventive ingenuity.

4.2 Claim 1 according to auxiliary request 4 is directed to a 2,3,8,9-tetrahydro-1,4-dioxino-indol-8-one compound having a dopamine D_2 receptor agonist activity (specification of the application page 7, line 56 to page 8, lines 4 and 23 to 27). Document (1), which is cited and acknowledged in the specification of the application on page 2, lines 5 to 19 as closest prior art, refers also to dopamine D_2 receptor agonists (page 4, line 19, page 7, line 1). This document describes 2,3-dihydro-1,4-dioxino-indol compounds which may be substituted with the radical $-(CH_2)_m-OR_2$ at the 8-position (claim 1 on page 29, line 22, claims 2 and 3) which radical may boil down to an OH-group (page 22, lines 25 and 30: m=0, R_2=H). That indol substituted with an OH-group, which is the enol-form, is chemically tantamount to the 8,9-dihydro-indol of claim 1

substituted with a carbonyl-group, which is the keto-form, due to the keto-enol tautomerism. This finding, though having been challenged at the beginning of the proceedings, was finally conceded by the Appellant at the oral proceedings before the Board.

4.2.1 The Appellant, however, disputed that the generic disclosure of document (1) described indols substituted with an OH-group. The definition of the index "m" necessary to arrive at an OH-group was purported to be missing for the radical $-(CH_2)_m-OR_2$ in that document.

The index "m" is found in eleven generic groups indicated in claim 1 of document (1) and is specified in that claim 1 on page 29, line 30 as being "0 to 6". Thus, there is no doubt that the index "m" is defined therein. The fact that this index is specified only once, but used in several generic groups does not alter that finding since, for the skilled reader, the only definition of "0 to 6" given for "m" then necessarily applies to any of the generic groups indicated in claim 1 of document (1), otherwise the whole claim would make no sense at all. Therefore the Appellant's allegation is not supported by the facts.

4.2.2 The Appellant argued furthermore that it was not possible to prepare indols substituted with an OH-group at the 8-position using the preparation process specified in document (1) since the synthetic route indicated therein via intermediate azides did not work. In support of this allegation he provided a declaration of Mr Stack. Thus, document (1) did not comprise an enabling disclosure of OH-substituted 2,3-dihydro-1,4-

dioxino-indols, i.e. of a carbonyl substituted 2,3,8,9-tetrahydro-1,4-dioxino-indol.

Indeed, document (1) would not effectively disclose OH-substituted indols even though it encompasses their chemical structure, if the skilled person were unable to find out from the information given in that document or from common general knowledge how to obtain these compounds (see T 206/83, OJ EPO 1987, 5, point 2 of the reasons and T 26/85, OJ EPO 1990, 22, point 8 of the reasons). In the present case, when following the Appellant's allegation that the preparation process indicated in document (1) would not result in OH-substituted indols, then the issue arises whether or not the skilled person is able on the basis of common general knowledge to prepare the OH-substituted indols of that document. However, the specification of the present application already clarifies this issue in demonstrating that the skilled person needs no more than his general knowledge to arrive at those indols. Thus, this specification indicates on page 3, line 56 that those compounds "may be prepared by methods known *per se*" and specifies on page 6, lines 27 to 33 a well known synthetic route based on prepublished literature from 1974 for obtaining those particular indols. Therefore the Board concludes that a successful preparation of the OH-substituted indols of document (1) is within the available general knowledge and conventional for the skilled person with the consequence that this document comprises an enabling disclosure.

Any challenge by the Appellant of the above finding in respect of the enabling disclosure of document (1)

based on common general knowledge were mere speculation lacking substantiating facts or corroborating evidence. The burden of proving the facts it alleges lies with the party invoking these facts. If a party, whose arguments rest on these alleged facts, is unable to discharge its onus of proof, it loses thereby. In the absence of any pertinent evidence presented by him, the Appellant has not discharged the burden of proof which is upon him and, hence, the Appellant's view cannot convince the Board.

4.2.3 Thus, the Board considers, in agreement with the decision under appeal, that in the present case the 2,3-dihydro-1,4-dioxino-indol compounds described in document (1) represent the closest prior art and takes it as the starting point when assessing inventive step.

4.3 In view of this state of the art the problem underlying the patent in suit as submitted by the Appellant during the appeal proceedings consist in providing compounds having an improved activity profile, i.e. a better selectivity as to its dopamine D_2 receptor agonist activity.

4.4 To support his allegation that the purported improvement in selectivity of the dopamine D_2 receptor agonist activity is achieved by the claimed invention the Appellant submitted a test report annexed to the Statement of Grounds of Appeal. That comparative test report indicates and compares the test results of compounds according to the invention with those of one single comparative compound. The Appellant conceded at the oral proceedings before the Board that this particular comparative compound was just at hand at the

time when performing those test and, thus, was arbitrarily chosen by him.

It is the established jurisprudence of the Boards of Appeal that, to be relevant, comparative tests have to meet certain criteria. These include the proper choice of a comparative compound to be taken from the state of the art where only known substances - not notionally described ones - qualify for use in comparisons of compounds (decision T 181/82, OJ EPO 1984, page 401, point 7 of the reasons). In the present case the 2,3-dihydro-1,4-dioxino-indol compounds described in document (1) represent the closest piece of prior art (cf. point 4.2.3 above). That document, however, neither specifically discloses this comparative compound used in the Appellant's test report nor does it specify any of the particular structural elements comprised in that compound. Thus, the Appellant's comparative test report is unfair in not truly reflecting the subject-matter disclosed in the closest prior document (1). While showing in general a dopamine D_2 receptor agonist activity of the compounds according to the invention, the test report does not properly demonstrate that the purported improvement in selectivity of the claimed compounds has been successfully achieved vis-à-vis that state of the art. As a consequence, this test report is irrelevant and must be disregarded in the assessment of inventive step.

According to the jurisprudence of the Boards of Appeal, alleged but unsupported advantages cannot be taken into consideration in respect of the determination of the problem underlying the claimed invention (see decision T 20/81, OJ EPO 1982, 217, point 3, last paragraph of

the reasons). Since in the present case the alleged improvement, i.e. a better selectivity of the dopamine D_2 receptor agonist activity, lack the required adequate support, the technical problem as defined in point 4.3 above needs reformulation.

In view of the teaching of document (1), the objective problem underlying the invention is less ambitious and can only be seen in providing **further** compounds having a dopamine D_2 receptor agonist activity.

4.5 As the solution to this problem, the application proposes the 2,3,8,9-tetrahydro-1,4-dioxino-indol-8-one compound as defined in claim 1.

4.6 Finally, it remains to decide whether or not the claimed solution to this objective problem underlying the invention is obvious in view of the state of the art.

Document (1) specifically describes 2,3-dihydro-1,4-dioxino-indols having a dopamine D_2 receptor agonist activity. This basic structure may be substituted *inter alia* with an OH-group at the 8-position of the indol ring system being tantamount to the claimed indol-8-one structure (see point 4.2 above), and it may additionally be substituted with a substituted aminoalkyl group at the 2-position of the indol ring system (general formula on page 29 in combination with page 30, line 4), encompassing an aminomethyl group substituted with a benzyl group (page 29, line 30). Hence, document (1) covers the compound as defined in present claim 1.

The relevant question is, thus, whether the skilled person considering document (1) and being guided by the technical problem as defined in point 4.4 above would have been directed to the 2,3,8,9-tetrahydro-1,4-dioxino-indol defined in claim 1 as a further dopamine D_2 receptor agonist. The choice of an OH-group at the 8-position and of a benzylaminomethyl group at the 2-position of the indol ring system which results in the compound of claim 1, is within the ambit envisaged by the generic disclosure of document (1) which teaches that all the compounds covered by that document show this dopamine D_2 receptor agonist activity (page 2, lines 24 to 27). The presumption prevails, therefore, that the selected 2,3,8,9-tetrahydro-1,4-dioxino-indol of claim 1 will exhibit the same pharmacological activity as that compound represents an arbitrary selection out of a known class of active compounds. In the absence of evidence to the contrary, the Board concludes that faced with the problem indicated above, namely to provide merely further compounds having a dopamine D_2 receptor agonist activity, a skilled person would not require any inventive skill in picking out at random from structural variants outlined in document (1) the substitution of the basic 2,3-dihydro-1,4-dioxino-indol structure with an OH- and a benzylamino-methyl group thereby arriving without inventive ingenuity at the compound of claim 1, which is the solution proposed by the present application.

4.7 For these reasons, claim 1 is obvious in the light of the prior art document (1).

5. As a result, the Respondent's auxiliary request 4 is not allowable for lack of inventive step pursuant to Article 56 EPC.

6. The main request and auxiliary requests 1 to 3 covers the subject-matter of claim 1 of auxiliary request 4 in the form of the preferred embodiment according to their dependent claims 4 or 3, respectively. Therefore the considerations having regard to inventive step given in point 4.2 to 4.6 *supra* and the conclusion drawn in point 4.7 *supra* with respect to auxiliary request 4 applies also to the main request and auxiliary requests 1 to 3, i.e. their subject-matter claimed is obvious and does not involve an inventive step.

7. In these circumstances, the Appellant's main request and auxiliary requests 1 to 3 share the fate of auxiliary request 4 in that they too are not allowable for lack of inventive step pursuant to Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. Nuss