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D E C I S I O N
of 21 June 2005

Case Number: T 0563/01 - 3.3.1

Application Number: 97918935.4

Publication Number: 0915871

IPC: C07D 403/14

Language of the proceedings: EN

Title of invention:
Substituted bisindolylmaleimides for the inhibition of cell proliferation

Applicant:
F. Hoffmann-La Roche AG

Opponent:
-

Headword:
Bisindolylmaleimides/HOFFMANN-LA ROCHE

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Novelty (yes) - multiple selection"
"Inventive step (yes) - unexpected improvement - non-obvious solution"

Decisions cited:
-

Catchword:
-

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Case Number: T 0563/01 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 21 June 2005

Appellant: F. Hoffmann-La Roche AG
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Representative: Witte, Hubert, Dr.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 12 December 2000 refusing European application No. 97918935.4 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: J. M. Jonk
J. H. Van Moer

Summary of Facts and Submissions

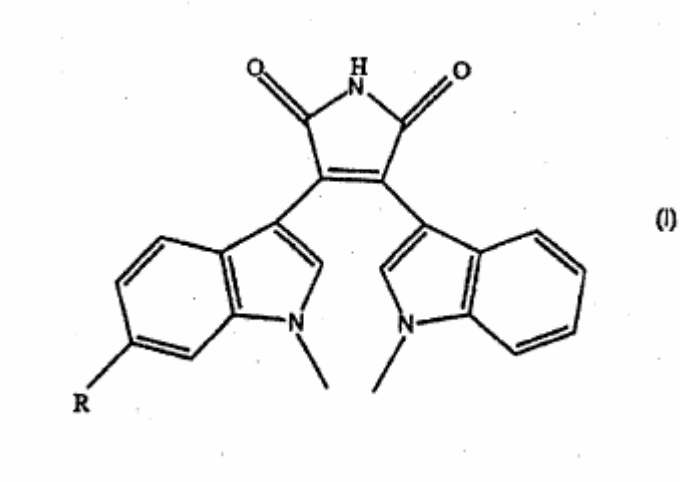
I. This appeal lies from the decision of the Examining Division refusing the present European patent application 97 918 935.4 (published under number WO 98/04553) relating to "substituted bisindolylmaleimides for the inhibition of cell proliferation".

II. The appeal lies from the decision of the Examining Division refusing the patent application on the ground that the subject-matter of Claims 1 to 3 filed on 30 September 2000 lacked inventive step in view of document:

(A) EP-A-0 328 026.

III. Claim 1 of said set of claims read as follows:

"A compound of the formula



(I)

wherein R is ethyl or pharmaceutically acceptable salts of compounds of formula I."

IV. The Examining Division held that the subject-matter of said set of claims was supported by the application as

filed within the meaning of Article 123(2) EPC and also that it was novel. However, it refused the patent application on the ground that the subject-matter of Claim 1 specified above lacked inventive step in view of document (A), since the claimed derivative and its salts represented a selection from the group of compounds disclosed in document (A) without showing any unexpected property.

V. Oral proceedings before the Board were held on 21 June 2005.

VI. The Appellant defended the patentability of the subject-matter of the present application on the basis of Claims 1 to 3 filed during the oral proceedings before the Board.

Claim 1 of this set of claims corresponded to Claim 1 forming the basis of the decision of the Examining Division, except that "ethyl" as the meaning of R in formula I was replaced by "unsubstituted C_1-C_5 alkyl".

During the oral proceedings he submitted a test-report to demonstrate that the compounds of present Claim 1 showed an improved anti-cell proliferative activity in comparison with closely related compounds of document (A). Moreover, he argued that the selection of the compounds of present Claim 1 from the large group of compounds of document (A) was not obvious to the skilled person.

VII. The Appellant requested that the decision under appeal be set aside, and that a patent be granted on the basis of the Claims 1 to 3 filed during the oral proceedings.

VIII. At the conclusion of the oral proceedings the Board's decision was pronounced.

Reasons for the Decision

1. The appeal is admissible.

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

2.1 Present Claim 1 is supported by Claim 1 of the application as filed in combination with the description as filed, page 2, lines 1 to 9.

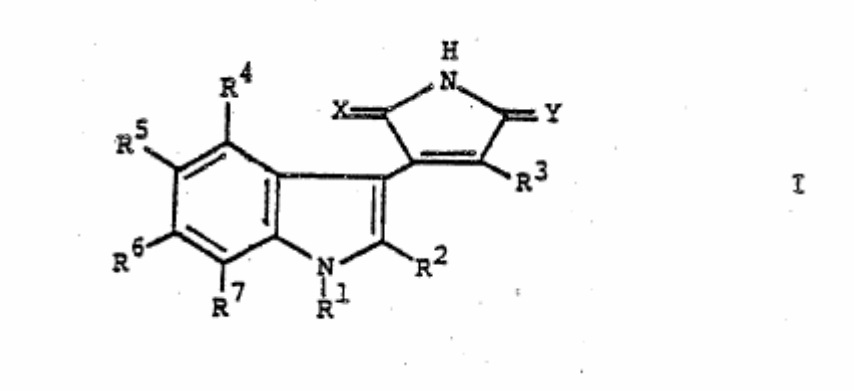
Claim 2 is supported by Claim 10 of the application as filed.

Claim 3 finds its support in Claim 11 of the application as filed in combination with the description as filed page 1, lines 13 to 18 and page 6, lines 20 to 25.

2.2 Therefore, the Board concludes that the subject-matter of Claim 1 of the present main request does not extend beyond the content of the application as filed, and consequently meets the requirement of Article 123(2) EPC.

3. *Novelty*

3.1 Document (A) discloses substituted pyrroles of the general formula



I

wherein

R^1 is hydrogen, alkyl, aryl, aralkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, trialkylaminoalkyl, aminoalkylaminoalkyl, azidoalkyl, acylaminoalkyl, acylthioalkyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, alkylsufinylalkyl, alkylsulfonylalkyl, alkylsulfonyloxyalkyl, alkylcarbonyloxyalkyl, cyanoalkyl, amidinoalkyl, isothiocyanatoalkyl, glucopyranosyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, hydroxyalkylthioalkyl, mercaptoalkylthioalkyl, arylthioalkyl or carboxyalkylthioalkyl or a group of formula

$-(CH_2)_n-W-Het$ (a) , $-(CH_2)_n-T-C(=V)-Z$ (b)

$-(CH_2)_n-NH-CO-Im$ (c) or $-(CH_2)_n-NH-C(=NH)-Ar$ (d)

wherein

Het is a heterocyclic group,

W is NH, S or a bond,

T is NH or S,

V is O, S, NH, NNO_2, NCN or $CHNO_2$,

Z is alkylthio, amino, monoalkylamino or dialkylamino,

Im is 1-imidazolyl,

Ar is aryl, and

n is a number of 2 to 6;

R^2 is hydrogen, alkyl, aralkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl, acylaminoalkyl, alkylsulfonylaminoalkyl, arylsulfonylaminoalkyl, mercaptoalkyl, alkylthioalkyl, carboxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylthio or alkylsulfinyl;

R^3 is a carbocyclic or heterocyclic aromatic group;

R^4, R^5, R^6 and R^7 are independently hydrogen, halogen, alkyl, hydroxyl, alkoxy, aryloxy, haloalkyl, nitro, amino, acylamino, monoalkylamino, dialkylamino, alkylthio, alkylsulfinyl or alkylsulfonyl; and

one of X and Y is O and the other one is O, S, (H,OH) or (H,H);

with the proviso that R^1 is not hydrogen if R^2 is hydrogen, R^3 is 3-indolyl or 6-hydroxy-3-indolyl, R^4, R^5 and R^7 are hydrogen, R^6 is hydrogen or hydroxyl and X and Y are both O;

as well as pharmaceutically acceptable salts of acid compounds of formula I with bases and of basic

compounds of formula I with acids (see page 2, line 1 to page 3, line 6).

The heterocyclic group R^3 in formula I as defined above can be a 5- or 6-membered heterocyclic aromatic group optionally containing a condensed benzene ring. Such a heterocyclic aromatic group can be optionally substituted and may be e.g. a 3-indolyl group as defined in formula I including the indicated meanings of R^1 to R^7 (see page 3, line 45 to page 4, line 13).

3.2 Thus, in order to arrive at the group of compounds as defined in present Claim 1, the skilled person would have to make a multiple selection from the compounds as defined in document (A) by formula I, namely, (i) the selection of a 3-indolyl group as R^3, (ii) a substitution of this group by methyl at the 1-position, (iii) the selection of methyl as R^1, (iv) the substitution of the benzene moiety of one of the two indolyl groups by an unsubstituted C_1-C_5-alkyl group, and (v) the substitution of this group at the 6-position as R^6.

3.3 In these circumstances, there is no direct and unambiguous disclosure in said prior art document of the claimed group of compounds and the Board concludes therefore that the claimed subject-matter is novel.

4. *Inventive step*

For deciding whether or not a claimed invention meets this criterion, the Boards of Appeal consistently apply the problem and solution approach, which essentially involves identifying the closest prior art, determining

in the light thereof the technical problem which the claimed invention addresses and successfully solves, and examining whether or not the claimed solution to this problem is obvious for the skilled person in view of the state of the art.

4.1 The Board considers, in agreement with the Appellant, that the closest prior art with respect to the subject-matter of Claim 1 of the application in suit is the disclosure of document (A).

4.2 This document discloses, as indicated above under point 3.1, a group of substituted pyrroles. Moreover, it discloses that the compounds of this group have anti-cell proliferative properties useful for the treatment of cancer (see page 9, lines 11 to 18).

4.3 Having regard to the Appellant's submissions with respect to the anti-cell proliferative properties of the compounds of the application in suit, the technical problem underlying the present application in the light of said closest prior art consist in providing compounds having improved properties for the treatment of cancer.

4.4 As the solution to this problem the present application proposes the group of compounds according to present Claim 1, which compounds are particularly characterised in that they have an unsubstituted C_1-C_5-alkyl group at the 6-position of one of the two indolyl groups.

4.5 To demonstrate that the claimed compounds of the present application have the purported improved properties, the Appellant relied on a test-report

submitted during the oral proceedings. This test-report shows that 3-(1,**6**-dimethyl-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dion of the application in suit, when compared to the closest exemplified compounds 3-(1,**5**-dimethyl-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dion and 3-(1,**7**-dimethyl-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dion of document (A) (see example 37, lines 29 and 30), has an unexpected superior anti-cell proliferative activity with respect to the cancer cell line MDA-MB435, namely, 0.01 **IC_{50}** (µm) instead of 0.41 IC_{50} (µm) and 1.46 IC_{50} (µm), respectively, in a first assay, and 0.04 **IC_{50}** (µm) instead of 0.35 IC_{50} (µm) and 1.45 IC_{50} (µm), respectively, in a second assay, as well as 0.05 **IC_{90}** (µm) instead of 0.97 IC_{90} (µm) and 2.72 IC_{90} (µm), respectively, in another first assay, and 0.04 **IC_{90}** (µm) instead of 0.87 IC_{90} (µm) and 5.09 IC_{90} (µm), respectively, in another second assay.

Therefore, the alleged improvement over the closest prior art has been successfully demonstrated and is credible for the whole scope of present Claim 1 in view of the nature of the lower alkyl substituents as claimed.

4.6 Finally, it remains to be decided whether or not the proposed solution to the problem underlying the application in suit is obvious in view of the cited prior art, i.e. document (A).

4.7 Although document (A), as indicated above under point 4.2, discloses a group of compounds having, like the compounds of the application in suit, anti-cell proliferative properties useful for the treatment of cancer, it cannot render the claimed subject-matter

obvious, since it does not give any incentive to the skilled person that the anti-cell proliferative properties useful for the treatment of cancer could be further improved by selecting the compounds of present Claim 1. In fact, document (A) clearly teaches that the most preferred compounds are those wherein the 2, 4, 5, 6 and 7 positions of the indolyl groups are unsubstituted (see page 4, lines 30 to 44).

4.8 Therefore, document (A) does not provide a pointer to the skilled person to arrive at the claimed solution of the above defined technical problem underlying the application in suit.

4.9 In conclusion, the Board finds that the subject-matter of present Claim 1 involves an inventive step in the sense of Article 56 EPC.

Moreover, the subject-matter of present Claim 2 relating to a composition comprising a compound of Claim 1 and an inert carrier, and that of present Claim 3 relating to the use of a compound of Claim 1 for the manufacture of a medicament for the treatment of cancer also involve an inventive step for the same reasons.

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 following documents:

   - Claims 1 to 3 filed at the oral proceedings.

   - A description yet to be adapted.

The Registrar: The Chairman:

N. Maslin A. Nuss