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**Datasheet for the decision
of 21 March 2007**

Case Number: T 1223/03 - 3.3.01

Application Number: 99924165.6

Publication Number: 1080092

IPC: C07C 487/04

Language of the proceedings: EN

Title of invention:

Bicyclic pyrimidines and bicyclic 3,4-dihydropyrimidines as
inhibitors of cellular proliferation

Applicant:

Warner-Lambert Company LLC

Opponent:

-

Headword:

Bicyclic Pyrimidines / WARNER-LAMBERT

Relevant legal provisions:

EPC Art. 54, 56

Keyword:

"Novelty (yes)"

"Inventive step (yes) - non obvious solution"

Decisions cited:

G 0001/03, G 0002/03

Catchword:

-



Case Number: T 1223/03 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 21 March 2007

Appellant: Warner-Lambert Company LLC
235 East 42nd Street
New York, NY 10017 (US)

Representative: Brunetti, Fabrizio
Pfizer
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 21 August 2003
refusing European application No. 99924165.6
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. Nuss
Members: C. M. Radke
D. S. Rogers

Summary of Facts and Submissions

- I. The appeal lies from the decision of the examining division by which the request to stay proceedings until the outcome of the cases G 01/03 and G 02/03 was rejected and the application was refused.

The examining division deemed the subject-matter of part of the claims not to be novel and the subject-matter of the remaining claims not to be based on an inventive step in view of any of the documents (D1) and (D2).

- II. The following documents were inter alia cited in the examination and appeal proceedings:

(D1) WO-A-95 19 774
(D2) US-A-5 654 307
(D4) WO-A-96 34 867.

- III. In the letter dated 10 December 2003 setting out the grounds for appeal, the Appellant argued that the examining division should have stayed the proceedings pending the outcome of Enlarged Board of Appeal cases G 01/03 and G 02/03, and he requested reimbursement of the appeal fee.

- IV. The Board issued a communication as an annex to the summons setting out its preliminary and non-binding opinion on why the examining division was not obliged to stay proceedings until the outcome of the cases G 01/03 and G 02/03 considering in particular that the claims on which the decision under appeal was based did not contain any disclaimer and thus did not depend

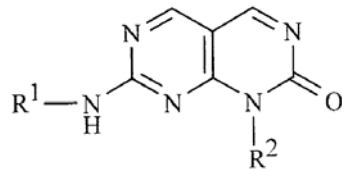
entirely on the outcome of the proceedings before the Enlarged Board of Appeal.

- V. The claims presently on file are claims 1 to 26 of the request submitted during the oral proceedings before the Board on 21 March 2007, with claims 1, 9, 10, 14, 18, 20 to 23, 25 and 26 as independent claims.

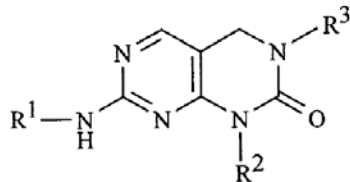
Independent claims 1 and 26 read as follows

"1. A compound selected from the group consisting of

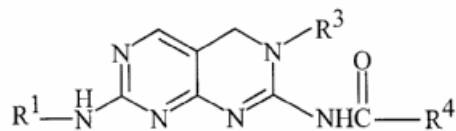
[a] compound of Formula I



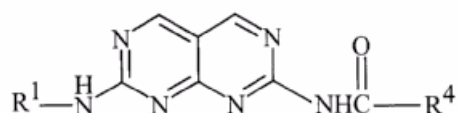
[b] compound of Formula II



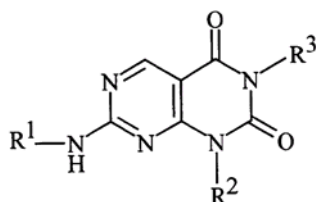
[c] compound of Formula III



[d] compound of Formula IV



[e] compound of Formula V



and the pharmaceutically acceptable salts thereof,
wherein:

R^1 , and R^2 are independently selected from the group
consisting of

H,

$(CH_2)_nAr$, wherein Ar is selected from the group of
phenyl, 3-chlorophenyl, 2,6-dibromophenyl, 2,4,6-
tribromophenyl, 1-naphtyl, 4,7-dichloro-2-naphtyl,
 COR^4 ,

$(CH_2)_n$ heteroaryl, wherein the heteroaryl have from 4 to
9 ring atoms, from 1 to 4 which are independently
selected from the group consisting of O, S and N, or is
selected from 2-pyridyl, 3-methyl-2-pyridyl, 3-
benzothienyl, 4-ethyl-2-benzothienyl, 2-furanyl, 3,4-
diethyl-2-furanyl, pyrrole, pyrazole, imidazole,
thiazole,

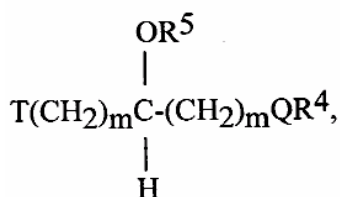
$(CH_2)_n$ heterocyclyl, wherein heterocyclyl means a
cycloalkyl group also bearing 1 to 3 heteroatoms
selected from O, S, or a group selected from
pyrrolidinyl, piperidyl, and morpholine,

C_1 - C_{10} alkyl,

C_3 - C_{10} cycloalkyl,

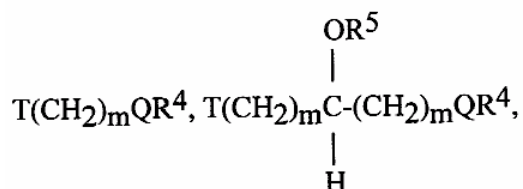
C_2 - C_{10} alkenyl, and

C_2-C_{10} alkynyl,
 wherein n is 0, 1, 2 or 3,
 and the $(CH_2)_nAr$, $(CH_2)_nheteroaryl$, alkyl, cycloalkyl,
 alkenyl, and alkynyl groups are optionally substituted
 by up to 5 groups selected from NR^4R^5 , $N(O)R^4R^5$, $NR^4R^5R^6Y$,
 alkyl, where alkyl is a straight or branched
 hydrocarbon radical having from 1 to 10 carbons,
 hydroxy
 alkoxy, wherein alkoxy is selected from the alkyl
 groups as defined above bound through oxygen, $-O-(CH_2)_2-$
 $O-CH_3$.
 phenoxy,
 thiol,
 thioalkyl, wherein the alkyl group is defined above,
 halo, wherein the halo is selected from fluoro, chloro,
 bromo and iodo,
 COR^4 , CO_2R^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 , aldehyde,
 nitrile, nitro,
 heteroaryloxy, wherein heteroaryl is selected from 2-
 pyridyl, 3-methyl-2-pyridyl, 3-benzothienyl, 4-ethyl-2-
 benzothienyl, 2-furanyl, 3,4-diethyl-2-furanyl,
 pyrrole, pyrazole, imidazole, thiazole,
 $T(CH_2)_mQR^4$,



$C(O)T(CH_2)_mQR^4$, $NHC(O)T(CH_2)_mQR^4$,
 $T(CH_2)_mC(O)NR^4NR^5$, or $T(CH_2)_mCO_2R^4$ wherein each m is
 independently 1-6, T is O , S , NR^4 , $N(O)R^4$, NR^4R^6Y , or
 CR^4R^5 , and Q is O , S , NR^5 , $N(O)R^5$, or NR^5R^6Y ;

R^3 has the meanings of R^2 , wherein R^2 is as defined above, as well as OH, NR^4R^5 , $COOR^4$, OR^4 , $CONR^4R^5$, $SO_2NR^4R^5$, SO_3R^4 , PO_3R^4 ,



wherein T and Q are as defined above;

R^4 and R^5 are each independently selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $N(C_1$ - C_6 alkyl) $_{1or2}$, $(CH_2)_nAr$, wherein Ar is as defined above, C_3 - C_{10} cycloalkyl, wherein cycloalkyl is as defined above, heterocyclyl, wherein heterocyclyl is as defined above, and heteroaryl, wherein heteroaryl is selected from 2-pyridyl, 3-methyl-2-pyridyl, 3-benzothienyl, 4-ethyl-2-benzothienyl, 2-furanyl, 3,4-diethyl-2-furanyl, pyrrole, pyrazole, imidazole, thiazole, or R^4 and R^5 together with the nitrogen to which they are attached optionally form a ring having 3 to 7 carbon atoms and said ring optionally contains 1, 2, or 3 heteroatoms selected from the group consisting of nitrogen, substituted nitrogen, wherein the substituents are selected from C_1 - C_{10} alkyl, $(CH_2)_nPh$ where n is 0, 1, 2, or 3, oxygen, and sulfur;

when R4 and R5 together with the nitrogen to which they are attached form a ring, the said ring is optionally substituted by 1 to 3 groups selected from OH, OR⁴, NR⁴R⁵, (CH₂)_mOR⁴, (CH₂)_mNR⁴R⁵, T-(CH₂)_mQR⁴, CO-T-(CH₂)_mQR⁴, NH(CO)T(CH₂)_mQR⁴, T-(CH₂)_mCO₂R⁴, or T(CH₂)_mCONR⁴R⁵, R⁶ is alkyl, wherein alkyl is defined above;

and

Y is a halo counter-ion, wherein halo is as defined above."

"26. A pharmaceutical formulation comprising a compound of anyone of claims 1 to 8 in combination with a pharmaceutically acceptable carrier, diluent, or excipient."

Independent claims 9, 14, 18, 20 to 23 and 25 are directed to uses of compounds of claims 1 to 8 for the preparation of medicaments for specific therapeutic purposes.

VI. The arguments of the Appellant in support of these claims can be summarised as follows:

The compounds claimed in present claim 1 are novel as they differ

- from those disclosed in document (D1) in that the present compounds do not have a bulky substituent at the carbon atom in position 4 of the pyrimidine ring as required by the general formulae I and II depicted on pages 7 and 10 of document (D1); and
- from those disclosed in document (D4) in that the present compounds have a pyrimido[4,5-*d*]pyrimidine core where the compounds disclosed in (D4) are substituted pyrido[2,3-*d*]pyrimidines.

If document (D1), or the respective US patent (D2), is to be considered as the closest prior art, the objective problem to be solved could be seen to be the provision of alternative, and possibly better compounds inhibiting cell proliferation. Documents (D1) and (D2) disclose pyrimido[4,5-*d*]pyrimidines only as one of many core structures of cell proliferation inhibiting compounds. The person skilled in the art would not have modified the pyrimido[4,5-*d*]pyrimidines in order to solve the problem mentioned above as the respective compounds disclosed in (D2) are shown to be among the least effective (see the IC₅₀ values of the products of examples 69 and 70 in Table 1 in columns 23 and 24).

- VII. During oral proceedings before the Board, the Appellant withdrew his request for reimbursement of the appeal fee.
- VIII. The Appellant requested that the decision under appeal be set aside and a patent be granted on the basis of the claims 1-26 of the request filed during oral proceedings before the Board.
- IX. At the conclusion of the oral proceedings the Board's decision was announced.

Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC*

Present claim 1 is based on original claims 1, 3, 7, 10, 12 and 15 and on page 11, lines 11-15; page 11, line 25 to page 12, line 2; page 12, lines 15-17; and page 13, lines 6-15 of the application as originally filed.

Present claims 2 to 26 are based on original claims 4-6, 8, 9, 13, 16, 25-41 and 43.

Hence the Board is satisfied that the amendments meet the requirements of Article 123(2) EPC.

3. Documents (D1) and (D2) both claim the same priorities and their disclosures as far as relevant for assessing novelty and inventive step of the subject-matter presently claimed is essentially the same. Hence it is sufficient to deal with one of these documents. In the following reference is made to document (D2) and not to document (D1).

4. *Novelty*

4.1 The heterocyclic ring system common to the compounds claimed in present claim 1 is a specific bicyclic ring system with four nitrogen atoms as heteroatoms in the rings, namely that of a pyrimido[4,5-*d*]pyrimidine which is optionally hydrogenated at positions 3 and 4.

4.2 Document (D2) discloses compounds having a pyrimido[4,5-*d*]pyrimidine ring system (see column 9, lines 39-47, examples 69 and 70 in columns 51 and 52, and Scheme 15 in column 65).

The compounds claimed in present claim 1 differ from those disclosed in document (D2) in that they are substituted at the 2 position by an oxygen atom or a group of the formula -NH-C(O)-R^4 whereas the compounds disclosed in document (D2) have no substituent at this position.

4.3 The Board is also satisfied that no other document cited during examination and/or appeal proceedings discloses any compounds defined in present claim 1.

4.4 For this reason, the subject-matter of independent claim 1 is novel. The same holds for claims 2-8 which are directed to preferred compounds covered by the formulae indicated in claim 1, for claims 9-25 which are directed to specific uses of these compounds, and for claim 26 directed to formulations containing these compounds.

Hence, the subject-matter of the present claims is novel.

5. *Inventive step*

In accordance with the "problem-solution" approach consistently applied by the Boards of Appeal, it is necessary, as a first step, to establish the closest state of the art which is normally a prior art document disclosing subject-matter conceived for the same

purpose or aiming at the same objective as the claimed invention and having the most relevant technical features in common.

5.1 The Board considers document (D2) as the closest prior art as it deals with the inhibition of cell proliferation as does the present application, and as document (D2) and not (D4) discloses compounds having a pyrimido[4,5-*d*]pyrimidine ring system (see (D2), column 1, lines 16-25; paragraph 4.2 above; document (D4), claim 1).

5.2 As next steps it has to be determined which technical problem was to be solved in view of the closest prior art and if this problem was indeed solved over the whole breadth of the subject-matter claimed.

Starting from the disclosure of document (D2), the least ambitious problem to be solved by the claimed compounds is the provision of alternative compounds inhibiting cell proliferation.

Tables 1 to 7 on pages 92-102 of the present application show that numerous compounds falling under the scope of present claim 1 do indeed inhibit cell proliferation.

Hence the Board is satisfied that this problem is indeed solved.

5.3 It remains to be decided whether or not the claimed solution to the technical problem mentioned above was obvious in view of the cited prior art taken as a whole.

5.3.1 The compounds described in document (D2) as cellular proliferation inhibitors all have to have a substituent of the formula $-X-(CHR_1)_n-Ar(R_2)_m$ at position 4 in the heteroaromatic pyrimidine ring, where Ar stands for a specific aryl or heteroaryl radical (see the general formulae I and II depicted in columns 3 and 5; see also column 4, lines 20-24).

Any compounds not having this radical at the 4-position of the pyrimidine ring are only disclosed in document (D2) as intermediates in multistep reactions in the later course of which said radical is introduced at the 4-position of the pyrimidine ring (see, e.g., column 65, lines 1-30).

There is no indication or hint in document (D2) that a compound devoid of this substituent at that position might have a cell proliferation inhibiting effect.

Therefore, the skilled person looking for alternative cell proliferation inhibitors would have deduced from document (D2) that a substituent of the formula $-X-(CHR_1)_n-Ar(R_2)_m$ or a substituent comparable to it in terms of sterical hindrance was required at position 4 of the pyrimidine ring.

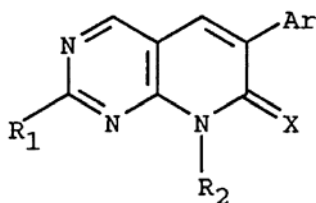
Consequently, a skilled person trying to solve the problem mentioned above would not have modified the teaching of document (D2) by completely omitting said substituent, and thus would not have ended up with the compounds of present claim 1 which have a hydrogen atom bonded to the carbon atom at position 4 of the heteroaromatic pyrimidine ring (or, as far as

formula IV is concerned, of any of the two condensed pyrimidine rings).

Therefore, document (D2) as such cannot render the subject-matter of present claim 1 obvious.

5.3.2 Even if the skilled person had combined the teachings of documents (D2) and (D4), what is unlikely, he would not have ended up with the compounds of present claim 1.

The compounds claimed in document (D2) have bulky groups at the carbon atom at position 4 of the pyrimidine ring (see point 5.3.1 above), whereas document (D4) relates to compounds of the formula



where Ar is a heteroaromatic or an optionally substituted phenyl group (see claim 1).

So, the compounds claimed in document (D4) also have a bulky group bonded to carbon atom of the bicyclic ring structure, i.e. the group Ar.

Hence, in view of the teaching of document (D4), a skilled person looking for alternative cell proliferation inhibitors would not have modified the compounds disclosed in document (D2) in such a way that they do not contain any bulky group bonded to a carbon atom of the bicyclic ring system. He would therefore not have arrived at the compounds as claimed in present claim 1.

- 5.4 For this reason, the subject-matter of present claim 1 is based on an inventive step.

The same holds for claims 2-8 which are directed to preferred compounds covered by the formulae indicated in claim 1, for claims 9-25 which are directed to specific uses of these compounds, and for claim 26 directed to formulations containing these compounds.

6. Hence, the subject-matter of the present claims is novel and involves an inventive step.

7. Remittal to the first instance

Although the Board has come to the conclusion that the request is to be allowed, the description still has to be brought into conformity with the claims. 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 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 to have the description adapted to the amended claims.

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 claims and a description to be adapted:

Claims Nos. 1-26 of the Request dated 21 March 2007 submitted at the oral proceedings.

The Registrar:

The Chairman:

N. Maslin

A. J. Nuss