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D E C I S I O N
of 22 January 2002

Case Number: T 0964/98 - 3.3.1

Application Number: 92104089.5

Publication Number: 0503563

IPC: C07D 473/06

Language of the proceedings: EN

Title of invention:
Novel 8-substituted purines as selective adenosine receptor agents

Applicant:
MERRELL PHARMACEUTICALS INC.

Opponent:
-

Headword:
Purines/MERRELL

Relevant legal provisions:
EPC Art. 56, 107
EPC R. 88

Keyword:
"Correction of Appellant's name in Notice of Appeal - Yes"
"Inventive step (yes) - after amendment of claims"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0964/98 - 3.3.1

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 22 January 2002

Appellant: MERREL PHARMACEUTICALS INC.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 11 May 1998 refusing European patent application No. 92 104 089.5 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: A. J. Nuss
Members: P. P. Bracke
S. C. Perrymann

Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision, dispatched on 11 May 1998, refusing European patent application No. 92 104 089.5, published as EP-A-0 503 563, due to lack of inventive step.

In particular, the Examining Division was of the opinion that a superior effect for the claimed compounds according to the requests underlying the decision had not been shown and that it could be deduced from the combined teaching of document

(1): US-A-4 968 672 or

(2): WO-A-86/02551 and

document

(4): J. Med. Chem. 1990, 33, pages 3127 to 3130

that the claimed compounds would have an A_1-adenosine receptor antagonistic activity.

II. In the notice of appeal of 17 July 1998 there was a heading "MERELL PHARMACEUTICALS INC", but the text began "On behalf of Hoechst Marion Roussel ... APPEAL ... is lodged ...".

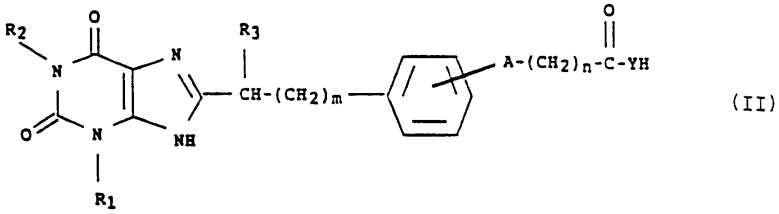
In a communication of 26 October 1998 according to Rule 65(2) EPC the Board informed the representative who drafted the notice of appeal that according to EPO records Merrell Pharmaceutical Inc. was the present applicant. As no transfer away from this corporation

appeared to have been applied for, pursuant to Rule 20(3) EPC only Merrell Pharmaceuticals Inc. would appear to be a party entitled to appeal for the purpose of Article 107 EPC.

With letter dated 3 November 1998 the representative declared that the reference to Hoechst Marion Roussel was a mistake in the notice of appeal and that the applicant was still Merrell Pharmaceuticals Inc. since a transfer of rights to Hoechst Marion Roussel had not yet taken place. Correction of the Notice of Appeal was thus requested under Rule 88 EPC.

III. With letter of 21 September 1998 the Appellant filed a set of claims, titled "Auxiliary Request 3", consisting of 4 claims reading:

"1. A compound of the formula II



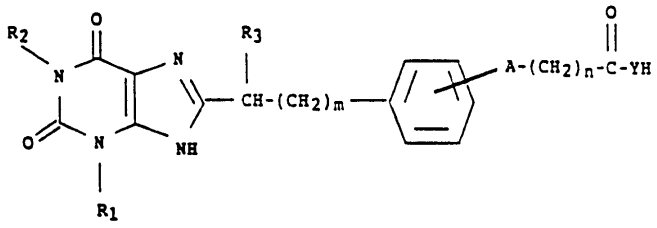
(II)

wherein

R_1 and R_2 are n-propyl, R_3 is methyl or ethyl

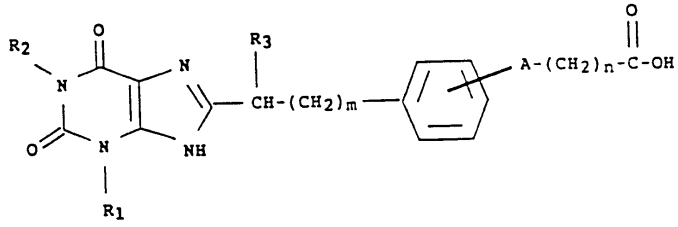
m is 0 or 1
A is O
n is 1
Y is $-NH(CH_2)_pNH-$ and
p is 2."

"2. A process for preparing compounds as defined in Claim 1



(II)

comprising amidating a compound of formula



with the appropriate amine, in which all the substituents are defined as above."

"3. A method of providing a pharmaceutical composition comprising combining a compound according to Claim 1 with a pharmaceutically acceptable carrier."

"4. A pharmaceutical composition comprising an effective amount of a compound of Claim 1 in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients."

IV. The Appellant argued that the claimed compounds essentially differed from those known from documents (1) and (2) by the presence of a $-CHR_3-(CH_2)_m-$ linking group between the phenyl ring and the 2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl moiety, that it could not be predicted which influence on the

affinity of adenosine receptors such linking group would have and that it could not be derived from the cited prior art documents that the claimed compounds would have an **A_1**-adenosine receptor **anta**gonistic activity.

V. The Appellant requested correction of the Notice of Appeal pursuant to Rule 88 EPC to read: "On behalf of Merrell Pharmaceuticals Inc. ... appeal ... is lodged ... , and the grant of a patent on the basis of Claims 1 to 4 of Auxiliary Request 3.

Reasons for the Decision

1. *Admissibility of the appeal*

In the absence of any clear indication to the contrary, a professional representative who was authorised to act for an Applicant adversely affected by a decision and then filed an appeal against this decision must be presumed to be acting on behalf of the very same Applicant that he acted for in the first instance proceedings, and not on behalf of someone else not entitled to appeal.

Given that in the heading of the Notice of Appeal the Applicant on record and sole party entitled to appeal had been correctly named, the Board can accept that the reference in the text of the Notice of Appeal to Hoechst Marion Roussel was a mistake and that the notice of appeal had indeed been filed on behalf of the Applicant on record, namely Merrell Pharmaceuticals Inc.

Consequently, it is appropriate for the Board to permit correction of the Notice of Appeal pursuant Rule 88 EPC.

The appeal accordingly complies with the requirements of Articles 106 and 108 and Rule 64(b) EPC.

2. *Article 123(2) EPC*

Claim 1 is supported by the formula (II) on page 4 of the application as filed and by the description of the preferred compounds in the second sentence on page 68 of the application as filed. Present Claims 2 and 3 concern the process, respectively the method, described in Claims 3 and 6 for the Contracting State ES of the application as filed and present Claim 4 relates to the pharmaceutical compositions described in the third paragraph of page 64 of the application as filed.

Consequently, Claims 1 to 4 meet the requirement of Article 123(2) EPC.

3. *Novelty*

After examination of the cited prior art documents, the Board has reached the conclusion that the claimed subject-matter was not described in any of those documents.

In particular, the claimed compounds differ from the compounds described in documents (1) and (2) by the presence of the $-CHR_3-(CH_2)_m-$ linking group between the phenyl ring and the 2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl moiety and they differ from the compounds described in document (4) by the presence of

a $-O-CH_2-CO-NH(CH_2)_2NH_2$ group on the phenyl ring.

As novelty was not disputed by the Examining Division, it is not necessary to give detailed reasons for this finding.

4. *Inventive step*

4.1 The "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objective as the claimed invention and having the most relevant technical features in common.

Since the patent in suit relates to compounds providing a selective A_1-adenosine receptor antagonistic effect (see page 2, lines 27 and 28 of the application in suit), only documents describing compounds providing a selective A_1-adenosine receptor antagonistic effect could qualify as representing the closest state of the art. As document (2) is the only cited prior art document which describes specific compounds providing a selective A_1-adenosine receptor antagonistic effect, only document (2) can serve, as the closest prior art, as a suitable starting point for evaluating the inventive merit of the invention.

From Table 1 of document (2) it is namely known that compound 6d "8-(4'-carboxymethyloxyphenyl)-1,3-dipropylxanthine-2-aminoethylamide" has an A_2/A_1 ratio of 41.0 and from page 10, line 36 to page 11, line 1, it is known that a compound is A_1-selective if the ratio A_2/A_1 ratio is high. Thus, it follows from document (2) that a compound differing from the claimed ones only by the absence of a $-CHR_3-(CH_2)_m-$ linking group between the 2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-

8-yl moiety and the phenyl ring has a selective A_1-adenosine receptor antagonistic effect.

4.2 As it is said in the application in suit that the claimed compounds provide a selective A_1-adenosine receptor antagonistic effect and that they are, therefore, useful in providing a cardiotonic effect in the treatment of patients suffering from congestive heart failure (see page 2, lines 27 to 29), starting from the disclosure of document (2) the problem underlying the invention must be seen in providing further compounds having a selective A_1-adenosine receptor antagonistic effect.

4.3 The application in suit claims to solve this problem by the compounds defined in Claim 1 (see point III above).

4.4 The first point to be considered in assessing inventive step is then whether it has been convincingly shown that by the compounds according to Claim 1 the problem underlying the patent in suit has effectively been solved.

Since, according to Table 1 of the application in suit the IC_{50} adenosine A_2 is higher than the IC_{50} adenosine A_1 for racemic N-(2-aminoethyl)-2[4-[2-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetamide, for its (+) and (-) enantiomers and for N-(2-aminoethyl)-2[4-[1-(2,3,6,9-tetrahydro-1,3-dipropyl-2,6-dioxo-1H-purin-8-yl)propyl]phenoxy]acetamide, the Board accepts that a credible case has been put forward that the claimed compounds have a selective A_1-adenosine receptor antagonistic effect.

4.5 Therefore, it remains to be decided, whether, in the light of the teachings of the cited documents, a skilled person seeking to solve the above-mentioned problem would have arrived at the claimed compounds in an obvious way.

Document (2), in general, concerns xanthines not having a $-CHR_3-(CH_2)_m-$ linking group between the 2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl moiety and the phenyl ring. As it is taught on page 19, lines 29 to 31, that "The effects on biological activities caused by modifications or functions distal from the primary pharmacophore in some cases are quite impressive", it is clear that A_2/A_1 ratio-data presented for compound 6d may not be considered to be representative for any compound having an analogous chemical structure. This becomes, in particular, clear when comparing the A_2/A_1 ratio-data of compound 6d, differing from the chemical structure of 6g by the presence of a $-O-CH_2CO-NH-NH_2$ group on the phenyl ring instead of a $-O-CH_2CO-NH-\mathbf{(CH_2)_2}-NH_2$ group. Thus, it could not be derived from document (2) that the claimed compounds would have a specific A_1-adenosine receptor antagonistic effect.

Also from document (1) only xanthines are known which have the phenyl ring directly bonded to the 8-carbon atom of the 2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl moiety. As document (1) is related to prodrugs of adenosine receptor ligands, in general, ie A_1- as well as A_2-adenosine receptor agonists and antagonists (see column 2, lines 61 to 66) and as it is specifically said in column 2, lines 36 to 39 that "the development of new adenosine receptor drugs (either agonist or antagonist) has been impeded by the

multiplicity of effects mediated by adenosine", also document (1) cannot give any hint how the adenosine-receptor affinity would be influenced by inserting a $-CHR_3-(CH_2)_m-$ linking group between the 2,3,6,9-tetrahydro-1,3-dialkyl-2,6-dioxo-1H-purin-8-yl moiety and the phenyl ring.

Document (4) describes in Table III the binding constants for 8-(phenylisopropyl)xanthines at A_1- and A_2-adenosine receptors. As, however, document (4) only describes 8-(phenylisopropyl)xanthines which are unsubstituted in the phenyl ring and as it is completely silent about the influence of phenyl-substituents on the affinity of adenosine receptors, also from this document a skilled person could not get any indication that the claimed compounds would have a specific A_1-adenosine receptor antagonistic effect.

4.6 Therefore, the Board comes to the conclusion that Claim 1 is not obvious in the light of the teachings of the available prior art.

Claims 2 to 4 derive their patentability from the same inventive concept.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The request pursuant to Rule 88 EPC for the Notice of Appeal to read Merrell Pharmaceutical Inc. instead of

Hoechst Marion Roussel, Inc. is granted.

3. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 4 filed with letter of 21 September 1998 as "auxiliary Request 3" and a description yet to be adapted.

The Registrar: The Chairman:

N. Maslin A. Nuss