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**Datasheet for the decision
of 22 December 2011**

Case Number: T 1236/08 - 3.3.01

Application Number: 05012144.1

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C07D 213/53, C07D 231/08,
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C07C 311/48

Language of the proceedings: EN

Title of invention:

Inhibition of p38 kinase using symmetrical and unsymmetrical
diphenyl ureas

Applicant:

Bayer HealthCare LLC

Headword:

Diphenyl ureas/BAYER HEALTHCARE

Relevant legal provisions:

EPC Art. 54

RPBA Art. 13(1)

Relevant legal provisions (EPC 1973):

-

Keyword:

"Main request and auxiliary request 1: Novelty (no)"

"Auxiliary request 2: not admitted - submitted at a late stage of the oral proceedings and not prima facie overcoming the objections"

Decisions cited:

-

Catchword:

-



Case Number: T 1236/08 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 22 December 2011

Appellant: Bayer HealthCare LLC
(Applicant) 555 White Plains Road
Tarrytown, NY 10591 (US)

Representative: Weiß, Wolfgang
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 25 February 2008
refusing European patent application
No. 05012144.1 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: P. Ranguis
Members: C. M. Radke
D. S. Rogers

Summary of Facts and Submissions

- I. European patent application no. 05 012 144.1 was filed as a divisional of European patent application no. 98 964 221.0, and claims the priority of US patent application no. 08/995 749 filed on 29 December 1997.
- II. The present application relates to certain urea derivatives and to their use for the treatment of diseases mediated by cytokines and proteolytic enzymes.
- III. The appeal lies from the examining division's decision to refuse the application.
- IV. Document
- (D1) WO-A-98/52 558
- was cited during the examination proceedings.
- V. The examining division held that the replacement of the use claims initially filed with the present divisional application by product claims was an abuse of procedure. The filing of the initial claims resulted in a refund of the search fee, whereas the present product claims required an additional search.

The examining division stated that the claims then on file did not enjoy the priority claimed. Therefore, document (D1) formed part of the state of the art under Article 54(2) EPC. The problem solved in view of document (D1) was the provision of further urea derivatives. In the light of the extremely close structural relationship to the compounds of document

(D1) and due to the absence of comparative tests, the subject-matter claimed was obvious.

VI. The present decision is based on the following claims:

The claims of the main request and of auxiliary requests 1 and 2, all submitted during the oral proceedings of 22 December 2011.

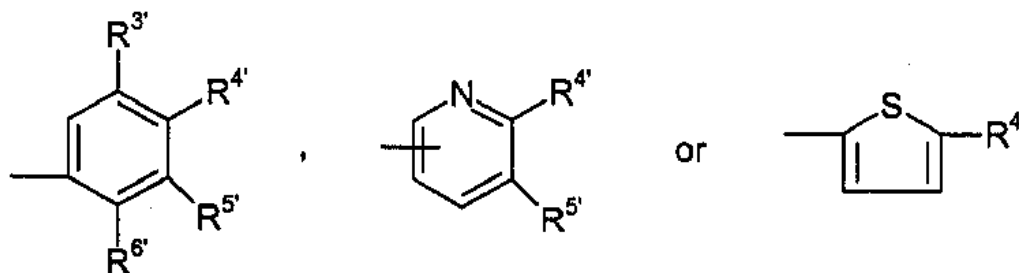
(a) The claims of the main request read as follows:

"1. A compound of formula I



wherein

A is



B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, wherein if B is substituted, it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and each W is independently

selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{NO}_2$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ -alkenyl, $\text{C}_1\text{-C}_{10}$ -alkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_3\text{-C}_{13}$ heteroaryl, $\text{C}_4\text{-C}_{23}$ alkheteroaryl, substituted $\text{C}_1\text{-C}_{10}$ alkyl, substituted $\text{C}_2\text{-C}_{10}$ -alkenyl, substituted $\text{C}_1\text{-C}_{10}$ -alkoxy, substituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, substituted $\text{C}_4\text{-C}_{23}$ alkheteroaryl and Q-Ar;

wherein if W is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of $-\text{CN}$, $-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, NO_2 , $-\text{NR}^7\text{C}(\text{O})\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$ and halogen up to per-halo;

wherein each R^7 is independently selected from H, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_2\text{-C}_{10}$ -alkenyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_6\text{-C}_{14}$ aryl, $\text{C}_3\text{-C}_{13}$ hetaryl, $\text{C}_7\text{-C}_{24}$ alkaryl, $\text{C}_4\text{-C}_{23}$ alkheteroaryl, up to per-halosubstituted $\text{C}_1\text{-C}_{10}$ alkyl, up to per-halosubstituted $\text{C}_2\text{-C}_{10}$ -alkenyl, up to per-halosubstituted $\text{C}_3\text{-C}_{10}$ cycloalkyl, up to per-halosubstituted $\text{C}_6\text{-C}_{14}$ aryl and up to per-halosubstituted $\text{C}_3\text{-C}_{13}$ hetaryl,

wherein Q is $-\text{O}-$, $-\text{S}-$, $-\text{N}(\text{R}^7)-$, $-(\text{CH}_2)_m-$, $-\text{C}(\text{O})-$, $-\text{CH}(\text{OH})-$, $-(\text{CH}_2)_m\text{O}-$, $-\text{NR}^7\text{C}(\text{O})\text{NR}^7\text{R}^7-$, $-\text{NR}^7\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^7-$, $-(\text{CH}_2)_m\text{S}-$, $-(\text{CH}_2)_m\text{N}(\text{R}^7)-$, $-\text{O}(\text{CH}_2)_m-$, $-\text{CHX}^a$, $-\text{CX}^a_2-$, $-\text{S}-(\text{CH}_2)_m-$ and $-\text{N}(\text{R}^7)(\text{CH}_2)_m-$,

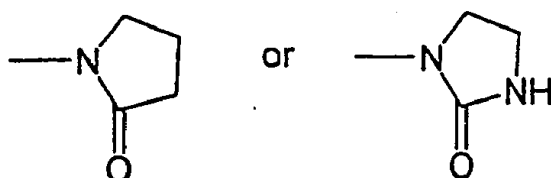
$m = 1\text{-}3$, and X^a is halogen; and

Ar is a 5-10 member aromatic structure containing 0-2 members of the group consisting of nitrogen, oxygen and sulfur, which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1} , wherein $n1$ is 0 to 3 and each Z is independently selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-C(O)-NR^7$, $-COR^7$, $-NO_2$, $-OR^7$, $-SR^7$, $-NR^7R^7$, $-NR^7C(O)OR^7$, $-NR^7C(O)R^7$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} hetaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl; wherein the one or more substituents of Z

is selected from the group consisting of $-CN$, $-CO_2R^7$, $-C(O)NR^7R^7$, $-OR^7$, $-SR^7$, $-NO_2$, $-NR^7R^7$, $-NR^7C(O)R^7$, $-NR^7C(O)OR^7$,

$R^{3'}$, $R^{4'}$, $R^{5'}$ are each independently H, C_{1-10} -alkyl, optionally substituted by halogen, up to perhalo, C_{1-10} alkoxy, optionally substituted by halogen, up to perhaloalkoxy, halogen; NO_2 or NH_2 ;

$R^{6'}$ is H, C_{1-10} -alkyl, C_{1-10} alkoxy, $-NHCOR^1$; $-NR^1COR^1$; NO_2 ;



one of $R^{4'}$, $R^{5'}$ or $R^{6'}$ can be $-X-Y$, or 2 adjacent $R^{4'}$ - $R^{6'}$ can together be an aryl or hetaryl ring with 5-12 atoms, optionally substituted by C_{1-10} -alkyl, C_{1-10} alkoxy, C_{3-10}

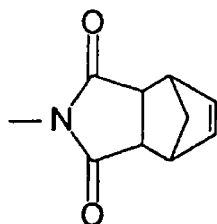
cycloalkyl, C₂₋₁₀ alkenyl, C₁₋₁₀ alkanoyl, C₆₋₁₂ aryl, C₅₋₁₂ hetaryl or C₆₋₁₂ aralkyl;

R¹ is C₁₋₁₀-alkyl optionally substituted by halogen, up to perhalo;

X is -CH₂-, -S-, -N(CH₃)-, -NHC(O)-, -CH₂-S-, -S-CH₂-, -C(O)-, or -O-; and

X is additionally a single bond where Y is pyridyl;

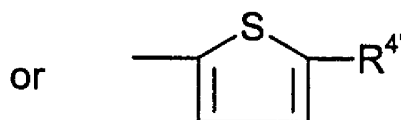
Y is phenyl, pyridyl, naphthyl, pyridone, pyrazine, benzodioxane, benzopyridine, pyrimidine or benzothiazole, each optionally substituted by C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, halogen, OH, -SCH₃ or NO₂ or, where Y is phenyl, by



or a pharmaceutically acceptable salt thereof, for use as a medicament for treating cancer."

"2. Pharmaceutical composition comprising a compound of claim 1 and a physiologically acceptable carrier."

(b) The claims of auxiliary request 1 only differ from the ones of the main request in that



was deleted as an alternative formula for the group A in claim 1.

(c) The claims of auxiliary request 2 only differ from the ones of the main request in that in claim 1 the following meanings of the radical W were deleted:

$-\text{CO}_2\text{R}^7$, $-\text{C}(\text{O})\text{NR}^7\text{R}^7$, $-\text{C}(\text{O})-\text{R}^7$, $-\text{OR}^7$,
 $-\text{SR}^7$, $-\text{NR}^7\text{R}^7$, $-\text{NR}^7\text{C}(\text{O})\text{OR}^7$, $-\text{NR}^7\text{C}(\text{O})\text{R}^7$.

VII. The board introduced the following documents during the appeal proceedings:

(D2) WO-A-96/25 157

(D3) US-A-3 214 468.

VIII. The board issued a first communication dated 15 April 2011 and annexed a second communication to the summons to oral proceedings dated 3 August 2011. In these communications it doubted, *inter alia*, that the subject-matter of the claims then on file was novel.

IX. The appellant considered the subject-matter of the claims of the main request and of auxiliary requests 1 and 2 to be novel as

- the compounds disclosed in document (D1) did not fall under the scope of the formula of present claim 1, and
- none of the documents (D2) and (D3) disclosed the use compounds for the treatment of cancer.

The reference to the inhibition of the melanoma growth stimulating activity on page 1 of document (D2), so the appellant continued, did not disclose the suitability of the compounds for treating cancer as the first paragraph on page 2 stated that the chemokines to be inhibited also were implicated in angiostasis.

- X. The appellant requested that the decision under appeal be set aside and a patent be granted in the following version:
Claims 1 and 2 of the main request or claims 1 and 2 of either auxiliary requests 1 or auxiliary request 2, all requests having been submitted at the oral proceedings before the board on 22 December 2011.
- XI. The board decided not to admit auxiliary request 2 into the proceedings. At the end of the oral proceedings the chairman announced the decision of the board.

Reasons for the Decision

1. The appeal is admissible.
2. Novelty / main request and auxiliary request 1
 - 2.1 Document (D2) discloses the following compounds in claim 13:

N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxyphenyl)urea;

N-(2-Hydroxy-4-nitrophenyl)-N'-(2-methoxy-3-chlorophenyl)urea;

N-(2-Hydroxy-4-cyanophenyl)-N'-(2-methoxyphenyl)urea;

N-(2-Hydroxy-4-cyanophenyl)-N'-(2-methylphenyl)urea;

N-(2-Hydroxy,3,4-dichlorophenyl)-N'-(2-methoxyphenyl)urea

(see page 101, line 33, and page 102, lines 2, 10, 13 and 22).

It was not disputed that these five compounds fall under the scope of formula I as defined in claim 1 of the main request and of auxiliary request 1

- where A corresponds to the first formula, in which R^{6'} is methoxy or methyl, and R^{5'} is hydrogen or chlorine; and
- B is a phenyl group substituted by a hydroxy group and chlorine atoms, a nitro or a cyano group.

2.2 It was, however, disputed, whether or not document (D2) also discloses the use as a medicament for treating cancer.

The document discloses that these compounds are to be used "in treating IL-8, GRO α , GRO β , GRO γ and NAP-2 mediated diseases" (see page 1, lines 7-9). Furthermore, it mentions on lines 23-24 of the same page: "For instance GRO α , β , γ have been referred to as MGSA α , β and γ respectively (**Melanoma** Growth Stimulating Activity)." (Emphasis added).

The appellant pointed out that document (D2) also disclosed that "the ELR chemokines (those containing the amino acids ELR motif just prior to the CXC motif) have also been implicated in angiostasis. Strieter et al, Science 258, 1798(1992)." (see page 2, lines 3-5). It concluded that compounds binding to the receptor of these chemokines might favour angiogenesis and thus tumour growth.

However, the expression "implicated in angiostasis" does not necessarily mean that these chemokines favour angiostasis; it could also mean that they inhibit

angiostasis. Therefore, the appellant's argument is not convincing.

Hence, there is no reason to believe that the reference to the implication in angiostasis would have deterred the person skilled in the art from using the compounds claimed in document (D2) for the treatment of melanoma.

For these reasons, the board concludes that document (D2) discloses the use of the compounds claimed for blocking the melanoma growth stimulating activity of the GRO α , β , and γ chemokines, and thus the use for treating melanoma, i.e. a type of cancer.

2.3 Hence, document (D2) discloses the use of compounds falling under the scope of formula I of claim 1 of the main request and of auxiliary request 1 as a medicament for the treatment of cancer. Consequently, the subject-matter of these claims is not novel. The same applies to claim 2 of both requests which relate to compositions containing these compounds and a physiologically acceptable carrier (see claim 30 of document (D2)).

2.4 For these reasons, the board refused the main request and auxiliary request 1.

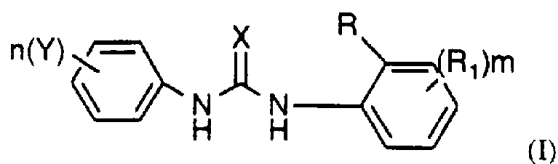
3. Auxiliary request 2

This request was submitted during the oral proceedings after the board had expressed its opinion that the subject-matter of the claims of the main request and of auxiliary request 1 lacked novelty.

According to Article 15(1) of the Rules of Procedure of the Boards of Appeal "Any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the Board's discretion." (see the Supplement to OJ EPO 1/2011, 39).

The claims of auxiliary request 1 differ from the ones of the main request in that numerous meanings of the radical W were deleted in order to render their subject-matter novel (see point VI (c) above).

First of all it was not immediately evident if the amended claims met the requirement under Article 123(2) EPC. Secondly, these amendments sought to delete the compounds of formula (I) of claim 1 of document (D2)



wherein

"R is any functional moiety having an ionizable hydrogen and a pKa of 10 or less" as required in said claim.

These amendments did, however, not result in the deletion of all these groups, inter alia because in present claims 1 any of the groups W and Ar may still be substituted by a group of the formula -COOR⁷ where R⁷ is a hydrogen atom. Therefore, it was not prima facie evident that these amendments could establish novelty.

Hence, the board decided not to admit the claims of auxiliary request 2 into the proceedings.

4. For the reasons given above, the subject-matter of the claims of the main request and of auxiliary request 1 is not novel. Auxiliary request 2 was not admitted into the proceedings. Consequently, the appeal is to be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

M. Schalow

P. Ranguis