BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [ ] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 22 September 2009

Case Number: T 1054/06 - 3.3.01

Application Number: 98925041.0

Publication Number: 1001945

IPC: C07D 241/52

Language of the proceedings: EN

Title of invention:
Quinoline and quinoxaline compounds which inhibit platelet-derived growth factor and/or p56Ick tyrosine kinases

Applicant:
Aventis Pharmaceuticals Inc.

Opponent:
-

Headword:
Quinoxaline derivatives/AVENTIS PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 123(2), 111(1), 84, 83

Relevant legal provisions (EPC 1973):
-

Keyword:
"Amendments - allowable (yes)"
"Clarity - (yes)"
"Sufficiency of disclosure (yes)"
"Remittal"

Decisions cited:
T 0615/95, T 0680/93, T 0068/85

Catchword:

-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1054/06 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 22 September 2009

Appellant: Aventis Pharmaceuticals Inc.
55 Corporate Drive
Bridgewater
NJ 08807 (US)

Representative: Adamson Jones
BioCity Nottingham
Pennyfoot Street
Nottingham NG1 1GF (GB)

Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 22 December 2005 refusing European application No. 98925041.0 pursuant to Article 97(1) EPC.**

Composition of the Board:

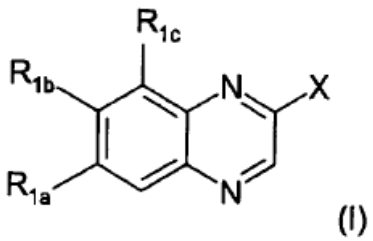
Chairman: P. Ranguis
Members: J.-B. Ousset
C.-P. Brandt

Summary of Facts and Submissions

I. This appeal lies from the decision of the examining division to refuse the European patent application EP-A-98 925 041.0, which was published as WO-A-98/54158.

II. Claim 1 of the refused request reads as follows:

"1. A compound of the formula (I)



(I)

wherein
X is L_2Z_2
L_2 is $(CR_{3a}R_{3b})_pZ_4$-$(CR_{3'a}CR_{3'b})_q$ or ethenyl;
Z_2 is
(i) a non-aromatic monocyclic or multicyclic ring system of 3 to 10 carbon atoms (hereinafter referred to as "cycloalkyl");
(ii) a non-aromatic monocyclic or multicyclic ring system containing a carbon-carbon double bond and having 3 to 10 carbon atoms (hereinafter referred to as "cycloalkenyl");
(iii) a 4- to 10-member monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is chosen from amongst nitrogen, oxygen and sulfur (hereinafter referred to as "heterocyclyl");
or
(iv) a 4-to 10-member monocyclic or multicyclic ring system which is partially saturated and wherein one or

more of the atoms in the ring system is chosen from amongst nitrogen, oxygen or sulfur (hereinafter referred to as "heterocyclenyl");
any of which is optionally substituted by S_1;
Z_4 is O, NR_4, S, SO, SO_2, or a bond;
p and q are independently 0,1,2,3 or 4, and p + q = 1,2,3, or 4 when Z_4 is a bond, and p + q = 0, 1, 2, or 3 when Z_4 is other than a bond;
R_{1a} and R_{1b} are, independently:
(i) an aliphatic hydrocarbon group which may be branched- or straight-chained, having 1 to 10 carbon atoms, and optionally substituted by S_2 (hereinafter referred to as "alkyl");
(ii) an aromatic carbocyclic radical containing 6 to 10 carbon atoms and optionally substituted by S_3 (hereinafter referred to as "aryl");
(iii) a 5- to 10-membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is nitrogen, oxygen or sulfur, optionally substituted by S_3 (hereinafter referred to as "heteroaryl")
(iv) hydroxy;
(v) H-CO-O- or alkyl-CO-O- (hereinafter referred to as "acyloxy");
(vi) an alkyl-O- group optionally substituted by S_4 (hereinafter referred to as "alkoxy");
(vii) a cycloalkyl-O- group optionally substituted by S_1 (hereinafter referred to as "cycloalkyloxy");
(viii) a heterocyclyl-O- group optionally substituted by S_1 (hereinafter referred to as "heterocyclyloxy");
(ix) a heterocyclyl-C(O)-O- group optionally substituted by S_1 (hereinafter referred to as "heterocyclylcarbonyloxy");

(x) an aryl-O- group optionally substituted by S_3 (hereinafter referred to as "aryloxy");
(xi) a heteroaryl-O- group optionally substituted by S_3 (hereinafter referred to as "heteroaryloxy");
(xii) cyano;
(xiii) R_5R_6N-; or
(xiv) acylR_5N-;
or one of R_{1a} and R_{1b} is hydrogen or halo and the other is alkyl, aryl, heteroaryl, hydroxy, acyloxy, alkoxy, cycloalkyloxy, heterocyclyloxy, heterocyclylcarbonyloxy, aryloxy, heteroaryloxy, cyano, R_5R_6N- or acylR_5N-;
- R_{1c} is hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyloxy, alkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, halo, cyano, R_5R_6N- or acylR_5N-;
S_1 is alkyl, hydroxy, acyloxy, alkoxy, halo, R_5R_6N-, acylR_5N-, carboxy or R_5R_6NCO- or a bivalent oxygen (-O-) on two adjacent carbon atoms to form an epoxide;
S_2 is alkoxy, halo, carboxy, hydroxy, or R_5R_6N-;
S_3 is hydrogen, hydroxy, halo, alkyl, alkoxy, carboxy, alkoxycarbonyl or Y_1Y_2NCO-, wherein Y_1 and Y_2 are independently hydrogen or alkyl;
S4 is amino, alkoxy, carboxy, alkoxycarbonyl, carboxyaryl, carbamoyl or heterocyclyl;
R_{3a}, R_{3b}, $R_{3a'}$ and $R_{3b'}$ are independently hydrogen or alkyl;
R_4 is hydrogen, alkyl or acyl; and
R_5 and R_6 are independently hydrogen or alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached form a heteroaryl group in which at least one nitrogen atom is present as a ring atom (hereinafter referred to as "azaheterocyclyl");

or an N-oxide thereof, hydrate thereof, solvate thereof, prodrug thereof, or pharmaceutically acceptable salt thereof."

III. The examining division decided that the presence of the expression "prodrugs" in claim 1 contravened the requirements of Articles 83 and 84 EPC. It contended that the definition given in the description for this word was not clear, since in the absence of any further definitions it did not clearly define the scope to be protected. No way of synthesis for the preparation of these prodrugs was mentioned in the description as originally filed and the person skilled in the art did not have any information as to how prepare these compounds. Moreover, a test allowing the person skilled in the art to test these prodrugs was also not disclosed in the description as originally filed. Hence, the person skilled in the art did not know, in the absence of information, which compounds fall under the scope of the claims and which test was to be used to predict whether after metabolisation, a compound will deliver the drug. The mere citation of "Pro-drugs as Novel Delivery systems" and "Bioreversible Carriers in Drug Design" could not be considered as a sufficient disclosure. The examining division found these disclosures as being the equivalent of a "research program" and concluded that the requirements of Article 83 EPC were not fulfilled.

IV. With his statement setting out the grounds of appeal, the appellant maintained the refused request and provided two auxiliary requests and argued that

- the term "prodrugs" was clear and had a well-established meaning in the field of medicinal chemistry. Its scope was also clear, since the person skilled in the art would recognize that any compound outside of the claimed scope but converted in vivo to a compound according to formula (I) of claim 1 was a prodrug of a compound of formula (I).

- based on Dr. Collis' declaration, which referred to citations in the books "Pro-drugs as Novel Delivery systems" and "Bioreversible Carriers in Drug Design", the person skilled in the art would readily recognize whether any particular compound would constitute a "prodrug". He, however, conceded that it was not possible to give an exhaustive and complete list of all possible "prodrugs".

- a reference-back to the decision T 68/85 (OJ EPO 1987, 228) was made in order to point out that not using the term "prodrug" would restrict in an unfair manner the scope of the invention.

V. In its annex to the summons to oral proceedings, the board noted in particular the following:

- due to the limitations carried out in the wording of the claims, the appellant was invited to point out the corresponding passages of the description, which justified such amendments. The appellant's attention was more particularly drawn to the groups L_2, Z_1 and X.

- the term "prodrug" in view of the documents cited may be understood as compounds which must be chemically transformed within the body to exert its pharmacological or therapeutic action. However, the question is whether this definition enables the person skilled in the art to identify without undue burden the compounds which are covered by the claimed subject-matter or, on the contrary, is simply a result to be achieved (Article 84 EPC). Likewise, the question is whether this definition gives the person skilled in the art sufficient guidance to find without undue burden the prodrugs of the compounds defined in Claim 1 appropriate to treat the mentioned diseases (Article 83 EPC).

  The board observes that document (5), namely G L Patrick, "An introduction to Medicinal Chemistry", second edition, pp. 239-250, seems to point out that when designing prodrugs, it is important to ensure that the prodrug is effectively converted to the active drug once it has been absorbed into the blood supply, but it is also important to ensure that any groups cleaved from the molecule are non-toxic (see page 239, bottom). In addition, the appellant should be prepared also to discuss all the information disclosed in the documents cited.

  If the board would come to the conclusion that one of the requests on file meets the requirements of Articles 123(2), 84 and 83 EPC, the case would be remitted to the first instance for further prosecution.

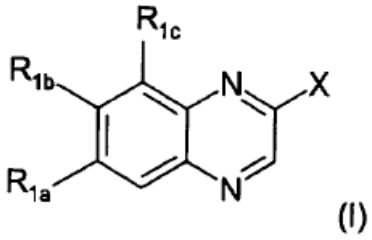
VI. With a further letter of 9 July 2009, the appellant withdrew the main and the auxiliary requests 1 and replaced them by a new main request and a new auxiliary request 1. Furthermore, he amended the auxiliary request 2 as filed with his statement setting out his grounds of appeal. He also supported the view that the limitation to X is L_2Z_2 and Z_1 is nitrogen did not contravene Article 123(2) EPC.

VII. The board issued a second communication, in which it gave the appellant the provisional reasons as to why the main and the auxiliary requests 1 and 2 contravened the requirements of Article 123(2) EPC.

VIII. With a fax of 16 July 2009, the appellant, still considering his main request as patentable, maintained it and filed as a precaution a new version of the auxiliary request 1 and a new version of the auxiliary request 2. He also mentioned that he would be prepared to accept either auxiliary request 1 or auxiliary request 2 if the board would confirm the remittal of the case to the first instance for further prosecution.

Claim 1 of this second auxiliary request, which contained fifteen claims, reads as follows:

"1. A compound of the formula (I)



(I)

wherein
X is L_2Z_2
L_2 is $(CR_{3a}R_{3b})_pZ_4$-$(CR_{3'a}CR_{3'b})_q$ or ethenyl;
Z_2 is
(i) a non-aromatic monocyclic or multicyclic ring system of 3 to 10 carbon atoms (hereinafter referred to as "cycloalkyl");
(ii) a non-aromatic monocyclic or multicyclic ring system containing a carbon-carbon double bond and having 3 to 10 carbon atoms (hereinafter referred to as "cycloalkenyl");
(iii) a 4- to 10-member monocyclic or multicyclic ring system wherein one or more of the atoms in the ring system is chosen from amongst nitrogen, oxygen and sulfur (hereinafter referred to as "heterocyclyl");
or
(iv) a 4-to 10-member monocyclic or multicyclic ring system which is partially saturated and wherein one or more of the atoms in the ring system is chosen from amongst nitrogen, oxygen or sulfur (hereinafter referred to as "heterocyclenyl");
any of which is optionally substituted by S_1;
Z_4 is O, NR_4, S, SO, SO_2, or a bond;
p and q are independently 0,1,2,3 or 4, and p + q = 1,2,3, or 4 when Z_4 is a bond, and p + q = 0, 1, 2, or 3 when Z_4 is other than a bond;
R_{1a} and R_{1b} are, independently:
(i) an aliphatic hydrocarbon group which may be branched- or straight-chained, having 1 to 10 carbon atoms, and optionally substituted by S_2 (hereinafter referred to as "alkyl");
(ii) an aromatic carbocyclic radical containing 6 to 10 carbon atoms and optionally substituted by S_3 (hereinafter referred to as "aryl");

(iii) a 5- to 10-membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is nitrogen, oxygen or sulfur, optionally substituted by S_3 (hereinafter referred to as "heteroaryl")
(iv) hydroxy;
(v) H-CO-O- or alkyl-CO-O- (hereinafter referred to as "acyloxy");
(vi) an alkyl-O- group optionally substituted by S_4 (hereinafter referred to as "alkoxy");
(vii) a cycloalkyl-O- group optionally substituted by S_1 (hereinafter referred to as "cycloalkyloxy");
(viii) a heterocyclyl-O- group optionally substituted by S_1 (hereinafter referred to as "heterocyclyloxy");
(ix) a heterocyclyl-C(O)-O- group optionally substituted by S_1 (hereinafter referred to as "heterocyclylcarbonyloxy");
(x) an aryl-O- group optionally substituted by S_3 (hereinafter referred to as "aryloxy');
(xi) a heteroaryl-O- group optionally substituted by S_3 (hereinafter referred to as 'heteroaryloxy');
(xii) cyano;
(xiii) R_5R_6N-; or
(xiv) acylR_5N-;
or one of R_{1a} and R_{1b} is hydrogen or halo and the other is alkyl, aryl, heteroaryl, hydroxy, acyloxy, alkoxy, cycloalkyloxy, heterocyclyloxy, heterocyclylcarbonyloxy, aryloxy, heteroaryloxy, cyano, R_5R_6N- or acylR_5N-;
- R_{1c} is hydrogen, alkyl, aryl, heteroaryl, hydroxy, acyloxy, alkoxy, cycloalkyloxy, heterocyclyloxy, aryloxy, heteroaryloxy, halo, cyano, R_5R_6N- or acylR_5N-;

S_1 is alkyl, hydroxy, acyloxy, alkoxy, halo, R_5R_6N-, acylR_5N-, carboxy or R_5R_6NCO- or a bivalent oxygen (-O-) on two adjacent carbon atoms to form an epoxide;
S_2 is alkoxy, halo, carboxy, hydroxy, or R_5R_6N-;
S_3 is hydrogen, hydroxy, halo, alkyl, alkoxy, carboxy, alkoxycarbonyl or Y_1Y_2NCO-, wherein Y_1 and Y_2 are independently hydrogen or alkyl;
S4 is amino, alkoxy, carboxy, alkoxycarbonyl, carboxyaryl, carbamoyl or heterocyclyl;
R_{3a}, R_{3b}, $R_{3a'}$ and $R_{3b'}$ are independently hydrogen or alkyl;
R_4 is hydrogen, alkyl or acyl; and
R_5 and R_6 are independently hydrogen or alkyl, or R_5 and R_6 taken together with the nitrogen atom to which they are attached form a heteroaryl group in which at least one nitrogen atom is present as a ring atom (hereinafter referred to as "azaheterocyclyl");
or an N-oxide thereof, hydrate thereof, solvate thereof, pharmaceutically acceptable salt thereof, or ketal, ester or zwitterionic thereof."

IX. With a fax sent on 17 July 2009, the board gave the appellant its provisional opinion as to the requests on file. The main request and auxiliary request 1 were still considered as contravening the requirements of Article 123(2) EPC but since the auxiliary request 2 was in agreement with these requirements and since the expression "prodrugs" was no longer present in the wording of the claims, the board let the appellant know that it intended to remit the case to the first instance to prosecute examination on the basis of this second auxiliary request. However, due to the presence of the main request and auxiliary request 1, oral proceedings were not cancelled.

X. With a fax dated of 17 July 2009, the appellant withdrew his main request and auxiliary request 1. He expected the oral proceedings to be cancelled and the case remitted to the first instance for further prosecution on the basis of the second auxiliary request (now main request, see point VIII) as filed on 16 July 2009.

XI. The board notified the appellant on 20 July 2009, that the oral proceedings were cancelled.

XII. The appellant requested that the decision under appeal be set aside and that the case be remitted to the first instance for further prosecution on the basis of the set of fifteen claims filed as auxiliary request 2 with letter of 16 July 2009 and now sole and main request.

Reasons for the Decision

1. The appeal is admissible.

Main request

2. Amendments

2.1 Since the wording of claim 1 of the main request has been amended, the board has to examine whether these amendments are in agreement with the requirements of Article 123(2) EPC, that is to say, whether current claim 1 contains technical information that the person skilled in the art would not have directly and unambiguously derived from the content of the

description as originally filed (see T 680/93, point 2 of the reasons, not published).

2.2 Claim 1 of the main request has been amended in the following way:

- the term "prodrug" present in the originally filed version of claim 1 has now been replaced by the expression "ketal, ester or zwitterionic form thereof". This amendment finds an unambiguous basis in the description as originally filed (see page 7, line 25).

- the compounds now claimed in the main set of claims are only quinoxaline derivatives. Such a limitation is supported by the content of the original description (see page 8, line 37).

- the values taken by the group X have been limited to the generic group L_2Z_2 by deletion of the value L_1 present in the original version of claim 1. This deletion does not amount to a singling out but rather maintains the subject-matter now claimed in claim 1 generic differing only for the original one by its size (see T 615/95, point 6 of the reasons).

- the generic values in the original version of claim 1 for the group Z_2 have been replaced by their corresponding values given in the description as originally filed (see page 5, lines 4 to 5 and 23 to 24 and page 6, lines 4 to 6 and 20 to 22 as well as their substituents on page 5, lines 7 to 8).

- the generic values in the original version of claim 1 for the groups R_{1a} and R_{1b} have been replaced by their corresponding values given in the description as originally filed (see from page 4, line 29 to page 7, line 23 including the respective substituents like S_1 on page 5,lines 7 to 8, S_2 on page 4, line 33, S_3 on page 5, lines 35 to 36 and S4 on page 6, lines 41 to 42). This also applies for the group R_{1c} (see page 4, lines 3 to 6).

- the values for the groups R_5 and R_6 are based on the pages 4, lines 9 to 10 in conjunction with page 6, lines 10 to 11 of the description as originally filed.

Compound claims 2 to 11 are all dependent of claim 1 and have a basis in the description as originally filed (see claims 46,62,77,78,83,84,86,90,91,96), claims 12 to 14 have a basis in the description as originally filed on page 33, lines 27 to 32 and claim 15 is based on the disclosure on page 34, lines 4 to 8 of the application as originally filed.

2.3 Therefore, the main request is in agreement with the requirements of Article 123(2) EPC.

3. Clarity

3.1 The expression "prodrug thereof" objected to by the examining division has been replaced in the wording of claim 1 by the expression "ketal, ester or zwitterionic form thereof".

3.2 The question to be answered is whether claim 1 comprising this feature complies with the requirements of Article 84 EPC.

3.3 Contrary to the expression "prodrug", a ketal as well as an ester or a zwitterionic form define the claimed compounds by structural features. These features are well-known by the person skilled in the art, who can immediately recognize the type of compounds to be enclosed in the ambit of claim 1.

3.4 The requirements of Article 84 are thus met by the main request.

4. Sufficiency of disclosure

4.1 In view of the description of the application as filed, the board is satisfied that the compounds defined in claim 1 may be prepared without undue burden (see schemes I-VIII) and that the tests disclosed render plausible that these compounds exhibit inhibition of cell proliferation and/or cell matrix production and/or cell movement via inhibition of PDGF-R tyrosine kinase activity so that they can be used in the treatment of various diseases as set out therein (see pages 33 to 42).

4.2 Furthermore, the person skilled in the art can, either on the basis of his own knowledge or by using the teachings of textbooks, make ketal and/or ester and/or zwitterionic forms of the compounds of formula (I) without undue burden.

4.3 The requirement of Article 83 EPC is, therefore met.

5. Remittal

5.1 The board has come to the conclusion that the reasons for refusing the application have been overcome. Having decided so, the board has not taken a decision on the complete case.

5.2 In view of the amendments carried out in the present request and in order not to deprive the appellant of the possibility to be heard by two instances, the board finds it appropriate to exercise its discretion under Article 111(1) EPC to remit the case to the first instance for further prosecution.

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 for further prosecution on the basis of the sole and main request currently on file.

The Registrar The Chairman

M. Schalow P. Ranguis