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D E C I S I O N
of 2 November 1998

Case Number: T 0853/94 - 3.3.2

Application Number: 89402315.9

Publication Number: 0356330

IPC: A61K 31/71

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition for inhibiting infection with virus causative of acquired human immunodeficiency syndrome

Applicant:
Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai

Opponent:
-

Headword:
Benanomicin A/ZAIDAN

Relevant legal provisions:
EPC Art. 52(1), 54(2), (3), (4), (5), 56, 167(2)(a)

Keyword:
"Novelty and inventive step: yes, claims restricted during appeal proceedings"
"Second medical use: no difference in substance between claims directed to the use of benanomicin A for the manufacture of a medicament for a new therapeutic application and claims directed to a process for the manufacture of the medicament for that new application using benanomicin A as an active ingredient"

Decisions cited:
G 0005/83, T 0958/94

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0853/94 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 2 November 1998

Appellant: Zaidan Hojin Biseibutsu Kagaku Kenkyu Kai
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 3 June 1994 refusing European patent application No. 89 402 315.9 pursuant to Article 97(1) EPC.**

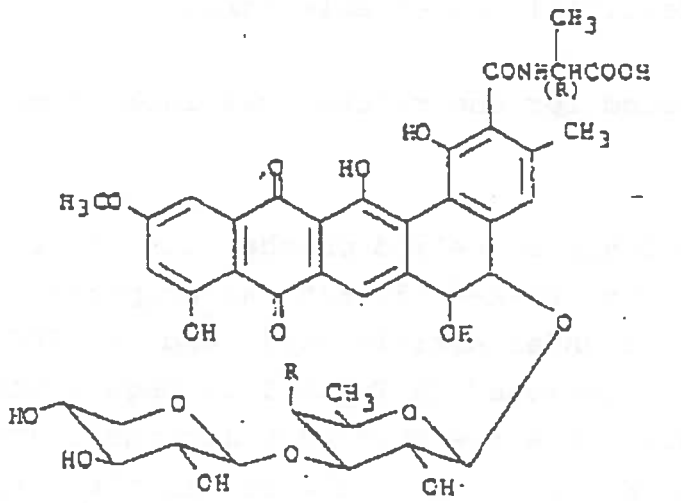
Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent application No. 89 402 315.9 filed on 21 August 1989 and published as EP-A 0 356 330 was refused under Article 97(1) EPC by the decision of the Examining Division dated 3 June 1994. The decision was based on claims 1 to 3 for all designated contracting states filed with the Applicant's letter dated 7 April 1992. These claims read as follows:

"1. Use of at least one of benanomicin A and benanomicin B having the formula



(I)

wherein R is a hydroxyl group for benanomicin A, or an amino group for benanomicin B, or salts thereof, in the manufacture of an antiviral pharmaceutical composition for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome.

2. Use of at least one of benanomicin A, benanomicin B and pharmaceutically acceptable salts thereof, as defined in claim 1, in the manufacture of an antiviral composition for inhibiting syncytium formation of human T-cells induced by a virus causative of acquired human immunodeficiency syndrome.

3. A process for the manufacture of an antiviral composition for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome, or for inhibiting syncytium formation of human T-cells induced by said virus, comprising mixing at least one of benanomicin A and benanomicin B, as defined in claim 1, or pharmaceutically acceptable salts thereof and a pharmaceutically acceptable carrier."

II. The stated ground for the refusal was lack of novelty of all claims.

The Examining Division relied on the content of document (2), viz. EP-A-0 351 625, as comprised in the state of the art under Article 54(3) and (4) EPC. It found that (2) disclosed in Table I on page 6 under the headline " Representative BU-3608 Compounds", *inter alia*, Compound No. 28747 and referred also to its use for preparing a pharmaceutical composition for inhibiting infection with HIV virus and inhibiting syncytium formation of human T-cells by HIV virus (see especially page 4, lines 19 to 22; page 7, lines 31 to 33; claims 1 to 6).

As far as the chemical structure and formula given in document (2) for Compound No. 28747 was concerned, the Examining Division referred to the earlier European patent application No. 88 101 410 [EP-A-0 277 621, document (3)] and, in particular, to the formula VII: BU-3608-C on page 6 of (3), which already showed the

correct formula and structure of the compound termed benanomicin B in the present application. Although, in contrast to formula VII given for compound BU-3608-C in document (3), the hydroxyl groups in positions 1 and 9 of the aromatic moiety and a further hydroxyl group in the sugar moiety were missing in the formula given for Compound No. 28747 in Table I of (2), the Examining Division concluded that it was immediately evident from the reference at the bottom of Table I in (2) to the earlier document (3) that by presenting the formula for Compound No. 28747 in Table I of (2) in reality nothing else would have been intended than to refer to the compound BU-3608-C corresponding to benanomicin B, in spite of certain errors in the said formula. On this basis the Examining Division considered the content of (2) prejudicial to the novelty of claims 1 and 2.

As far as claim 3 was concerned, the Examining Division was of the opinion that this claim was not drafted in accordance with the principles set out in decision G 5/83 (OJ EPO 1985, 64) and sought therefore not only to protect a 2nd or further medical use of benanomicin A and B but de facto to protect a process for the manufacture of pharmaceutical compositions comprising benanomicin A or B. The fact that pharmaceutical compositions comprising benanomicin A or B for a therapeutic use, different from that claimed in the present application, and a process for their preparation were already known from document (1), viz EP-A-0 315 147 (see especially page 2, lines 43 to 45; page 10, lines 15 to 52) led the Division to the conclusion that the particular intended use (therapeutical application) of the pharmaceutical compositions prepared by the process of claim 3 could not confer novelty on the claim having regard to the provisions of Article 54(5) EPC.

However, the Examining Division indicated already in the impugned decision that it considered the subject-matter of claims 1 and 2, if restricted to the use of benanomicin A only and its pharmaceutically acceptable salts, to be potentially patentable within the meaning of Article 52(1) EPC.

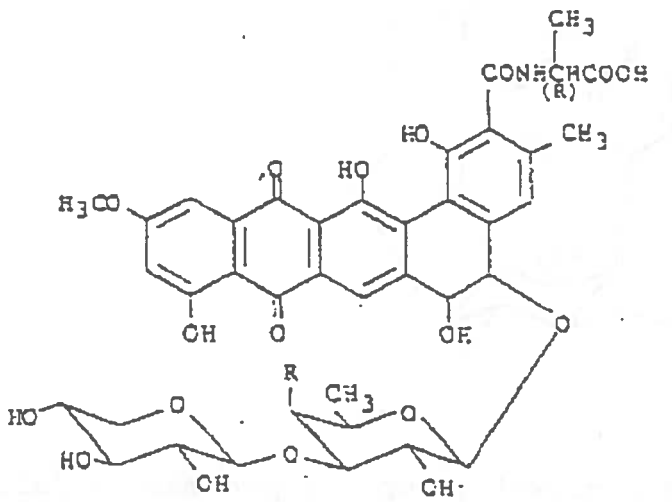
III. The Appellant filed an appeal against the above decision. In the statement of grounds the Appellant indicated its intention to continue this application without claiming the use of benanomicin B and deleted accordingly from claims 1 and 2 and the entire description but not from claim 3 the references to benanomicin B.

Following a Board's communication stating that claim 3 seemed to be inconsistent with claims 1 and 2 and the description as amended, the Appellant filed on 2 February 1998 an amended claim 3 from which the reference to benanomicin B had also been deleted.

IV. Following two further communications of the Board referring to certain observations as to the clarity and conciseness of the claims on file and the wording of the claims for the contracting state Spain, the Appellant requested with its reply dated 29 October 1998 that the decision under appeal be set aside and the patent be granted on the basis of the following documents:

(a) Claims 1 and 2 for all designated contracting states other than Spain submitted on 27 May 1998 reading as follows:

"1. Use of benanomicin A having the formula



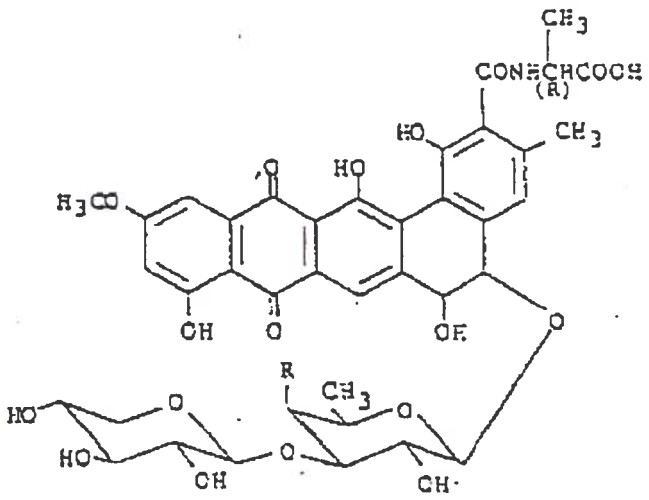
(I)

wherein R is a hydroxyl group, or salts thereof, in the manufacture of an antiviral pharmaceutical composition for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome.

2. Use of benanomicin A or pharmaceutically acceptable salts thereof, as defined in claim 1, in the manufacture of an antiviral composition for inhibiting syncytium formation of human T-cells induced by a virus causative of acquired human immunodeficiency syndrome".

(b) Claims 1 and 2 for the contracting state Spain submitted on 29 October 1998 reading as follows:

"1. A process for the manufacture of an antiviral composition for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome, comprising using, as an active ingredient of said composition, benanomicin A, having the formula



(I)

wherein R is a hydroxyl group, or pharmaceutically acceptable salts thereof.

2. A process for the manufacture of an antiviral composition for inhibiting syncytium formation of human T-cells induced by a virus causative of acquired human immunodeficiency syndrome, comprising using, as an active ingredient of said composition, benanomicin A or pharmaceutically acceptable salts thereof, as defined in claim 1.

(c) Description: pages 2 to 7, 9 to 28 submitted on 11 October 1994; pages 1, 8 submitted on 29 October 1998.

Reasons for the Decision

1. The appeal is admissible.

2. *Amendments*

2.1 Compared to the claims as originally filed relating to the use of both benanomicin A and benanomicin B, or pharmaceutically acceptable salts thereof as the pharmacologically active agents of pharmaceutical compositions for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome or for inhibiting syncytium formation of human T-cells induced by said virus, claims 1 and 2 presently on file for all designated contracting states other than Spain (hereinafter referred to as "the first set of claims") have been restricted during appeal proceedings to the use of benanomicin A only or pharmaceutically acceptable salts thereof for the above-mentioned purposes, in order to overcome the objection on the grounds of lack of novelty raised by the Examining Division.

2.2 Claims 1 and 2 for the contracting state Spain (hereinafter referred to as "the second set of claims") have similarly been restricted to a process for the manufacture of pharmaceutical compositions for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome or for inhibiting syncytium formation of human T-cells induced by said virus using benanomicin A only or pharmaceutically acceptable salts thereof as the pharmacologically active ingredients. The manufacturing process is disclosed from line 20 on page 13 to line 4 on page 15 of the originally filed documents.

2.3 The first and the second set of the amended claims and the consequential amendments to the description are therefore acceptable under the terms of Articles 123(2) and 84 EPC. The editorial amendment on page 8 of the description is similarly acceptable.

3. *Novelty*

3.1 Out of the documents cited in the examination proceedings under Article 54(2) or (3) EPC, the following relate in one way or another to compounds corresponding to the benanomicins as defined by formula (I) in paragraph I above:

Document (1), which forms part of the state of the art under Article 54(3) and (4) EPC, discloses the chemical structure of benanomicin A and benanomicin B (see especially pages 3 to 7, claims 1 to 4) and their antifungal and antibacterial activities (see especially page 2, lines 43 to 45; page 10, lines 15 to 52, claims 10 to 11).

Document (2) falls also under the terms of Article 54(3) and (4) EPC. It discloses in Table I on page 6 under the headline "Representative BU-3608 Compounds", *inter alia*, Compound No. 28747 and contains a reference to its use for preparing a pharmaceutical composition for inhibiting infection with HIV virus and inhibiting syncytium formation of human T-cells by HIV virus (see page 4, lines 19 to 22; page 7, lines 31 to 33; claims 1 to 6). However, irrespective whether or not Compound No. 28747 disclosed in (2) is, in view of the incorrectly drafted formula, indeed to be considered as referring to the compound benanomicin B, document (2) does not disclose or in any other way refer to the compound benanomicin A or its use in any therapeutic application.

Document (3) discloses, *inter alia*, on page 6 the compound VII: BU 3608 C which corresponds to benanomicin B but likewise does not disclose the compound benanomicin A or its use in any therapeutic application.

Both, document (4), viz. "The Journal of Antibiotics", vol. 41, No. 6, June 1988, pages 807 to 811, (see especially page 807, right-hand column; page 810, the paragraph bridging the left and right-hand column), and document (5), viz. "The Journal of Antibiotics", vol. 41, no. 8, August 1988, pages 1019 to 1028, (see especially page 1024), disclose the correct chemical structure of the compounds benanomicin A and benanomicin B and refer to their antifungal and limited antibacterial activities.

3.2 In view of the foregoing the conclusion must be drawn that the use of benanomicin A as an agent for inhibiting infection with a virus causative of acquired human immunodeficiency syndrome or for inhibiting syncytium formation of human T-cells induced by said virus is not disclosed in any cited prior art falling under the terms of Article 54(2) or (3) EPC. In accordance with the reasons and order of the decision G 5/83 (OJ EPO, 1985, 64), the Board therefore acknowledges that the subject-matter of the first set of claims is novel because of the hitherto undisclosed therapeutic application of benanomicin A. This is in agreement with the finding of the Examining Division.

3.3 In decision T 958/94 (OJ EPO 6/1997, 241), Board of Appeal 3.3.2 concluded that, in cases where a patent may be granted with claims directed to the use of a

known compound for a specified new and inventive therapeutic application (2nd or further medical use, see G 5/83, loc. cit.) such use may be claimed in the form

(i) either of the use of the compound for the manufacture of a medicament for the said therapeutic application

(ii) or of a process for the manufacture of a medicament for the said therapeutic application characterised in the use of the said compound.

It should be noted that in the case of decision T 958/94, both types of claim included an express reference to the specific second medical use. The Board stated in the said decision (see especially Reasons, point 3):

"Although the active substance per se, the medicament and the process for its manufacture were already known, the Enlarged Board in decisions G 1/83, G 5/83 and G 6/83 allowed a claim for preparing the medicament for the new therapeutic indication and directed to the substance's use in manufacturing the medicament intended for that new therapeutic indication.

In the same conditions - ie where the active substance, the medicament and the process for its manufacture all lack novelty - it would therefore be unjustified to regard a claim of the type "method for manufacturing the medicament intended for the new therapeutic indication" as not patentable, given that a claim for the use of a substance to manufacture a medicament intended for a new therapeutic use and a claim for a method of manufacturing the medicament intended for the new use and characterised in that the same substance is used are substantively equivalent."

The Board concluded further in the above-mentioned decision that there is no difference in substance whether the subject-matter of the claimed invention is defined in accordance with the form and wording mentioned under (i) above, or in accordance with the wording and form mentioned under (ii) above.

Moreover, the Board accepted in the said decision that one and the same application may contain one set of claims drafted in the form mentioned under (i) above and a second set of claims drafted in the form mentioned under (ii) above for contracting states which have entered reservations in accordance with Article 167(2)(a) EPC.

3.4 In the present case the Board sees no reason why the principles set forth above should not equally apply to the first and second sets of claims presently on file and considers these two sets of claims as equivalent in the sense outlined above. It follows, that the subject-matter of the second set of claims is also novel for the reasons given in paragraph 3.2 above.

4. *Inventive Step*

4.1 Documents (4) and (5) represent, in the Board's judgment, the closest prior art under Article 54(2) EPC since both these documents disclose the correct structure of the compound benanomicin A and refer already to its medical use as an antifungal and antibacterial agent. Given this closest state of the art, the technical problem the invention sets out to solve can only be seen as that of finding for benanomicin A further valuable properties in addition

to the ones specified in (4) and (5). In this respect it should be noted that the effort to find additional valuable properties and applications for a known physiologically active compound became over the recent years a rewarding and important task in the fields of pharmacology and pharmaceutical chemistry.

According to the claims, this problem is solved by the use of benanomicin A in the preparation of an antiviral agent for the particular therapeutic applications already mentioned in more detail in paragraph 3.2 (above). That the problem defined above has indeed been solved and benanomicin A exhibits indeed the desired pharmacological activities is plausibly derivable from the pharmacological tests described from line 24 on page 9 to line 13 on page 13 and, more specifically, from the tabulated test results from the Table on page 12 of the application as filed.

4.2 The finding that benanomicin A, which was known in the cited state of the art according to (4) and (5) to be effective only as an antibiotic, has also potent antiviral activity and, in particular, the finding that benanomicin A is capable of effectively inhibiting *de nuovo* infection of human T-cells with HIV, the causative agent of AIDS (cf. especially the results provided in the Table on page 12 of the application as filed), was, in the Board's opinion, at the priority date of the present application not obviously derivable, for a person skilled in the art, from the state of the art available to the Board.

It was similarly not foreseeable or predictable on the basis of the state of the art that benanomicin A would have the ability of inhibiting syncytium formation of

human T-cells after co-cultivation with HIV producing cells, suggesting that benanomicin A inhibits the attachment of HIV to human T-cells at an early stage of HIV-infection (see especially page 2, lines 11 to 14; page 12, line 11 to page 13, line 15 of the application as filed).

4.3 Document 3 refers extensively to the antifungal activity (cf. page 17, line 47, to page 20, end of Table VII) of the compounds BU-3608 (see formula V, page 4), BU-3608-B (see formula VI, page 6) and BU 3608-C (see formula VII, page 6, corresponding to benanomicin B), and mentions from line 46 on page 20 to line 5 on page 21 an antiviral activity of the compounds BU-3608 and BU-3608-B against herpes simplex virus type I and influenza virus A.

Apart from the fact that the structure of BU-3608 and BU-3608-B is different with respect to the sugar moiety from that of benanomicin A, their antiviral activity against the types of virus mentioned above does not, in the Board's judgment, suggest to a person skilled in the art, in the absence of any evidence to the contrary, that the infection of the human T-cells with the entirely different type of virus causative of acquired human immunodeficiency syndrome could successfully be inhibited under the action of benanomicin A.

4.4 In conclusion, there is, in the Board's view, presently no evidence available in the prior art cited in the search report indicating hat the skilled person, being aware of the antifungal and antibacterial activity disclosed for the benanomicins A and B in documents (4) and (5) and also being aware of the limited antiviral

activity disclosed for the compounds BU-3608 and BU-3608-B in document (3), could reasonably expect benanomicin A to be useful in effectively inhibiting infection of a susceptible living biological substrate with HIV and in inhibiting syncytium formation of human T-cells induced by said virus.

4.5 In view of the foregoing the Board concludes that the subject-matter of the first set of claims involves also an inventive step by virtue of the unexpected pharmacological properties and activities shown for benanomicin A in the present application. This is in agreement with the finding of the Examining Division.

4.6 Having regard to the conclusions reached in paragraph 3.3 (above), the criteria which lead the Board to acknowledge that the first set of claims involves an inventive step apply *mutatis mutandis* to the second set of claims for Spain.

Order

For these reasons it is decided that:

1. The decision of the Examining Division is set aside.

2. The case is remitted to the departement of the first instance with the order that a patent be granted on the basis of the following documents:

   (i) Claims 1 and 2 for all designated contracting states other than Spain as submitted on 27 May 1998;

   (ii) Claims 1 and 2 for the contracting state Spain as submitted on 29 October 1998;

   (iii) Description: pages 2 to 7, 9 to 28, as submitted on 11 October 1994; pages 1, 8, as submitted on 29 October 1998.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon