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Datasheet for the decision of 13 March 2007

Case Number: T 0998/04 - 3.3.01

Application Number: 95917310.5

Publication Number: 0755386

IPC: C07D 277/58

Language of the proceedings: EN

Title of invention:
Benzamide derivative, compositions containing said derivative and use thereof

Patentee:
Romark Laboratories, L.C.

Opponent:
Industriale Chimica S.R.L.

Headword:
Tizoxanide/ROMARK LABORATORIES

Relevant legal provisions:
EPC Art. 54(1)(2), 56, 114(2), 117

Keyword:
"Novelty (yes) - process of preparation disclosed in the prior art not inevitably leading to the claimed subject-matter - disclosed example not duplicated in every details"
"Prior use - not admitted into the proceedings as late-filed and not sufficiently relevant"
"Inventive step (no) - obvious solution"
"Requests under Article 117 EPC (no) - not consistent with the character of the post-grant opposition proceedings"

Decisions cited:
G 0009/91, T 0012/81, T 0181/82, T 0396/89, T 0441/90, T 0782/92, T 0955/96, T 0671/03

Catchword:
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Case Number: T 0998/04 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 13 March 2007

Appellant: (Opponent)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 13 July 2004 rejecting the opposition filed against European patent No. 0755386 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: A. Nuss
Members: P. Ranguis
D. S. Rogers

Summary of Facts and Submissions

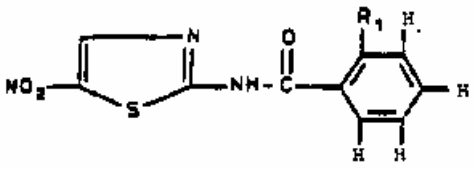
I. The present appeal lies from the decision of the Opposition Division to reject the opposition filed against the European patent No. 0 755 386 (European patent application No. 95 917 310.5).

II. For the purposes of this decision the following numbering will be used to refer to documents:

(1) Antimicrobial agents and Chemotherapy, vol. 12, No. 3, (1977), p. 353-356,
(2) US-A-3 950 351
(3) Experimental report submitted by F. Benigni dated 10 February 2003,
(4) Pre-clinical toxicology of Nitazoxanide - A new antiparasitic compound, Journal of Applied Toxicology, Vol. 5, No. 2, (1985), p. 49-52,
(5) declaration under oath of J-F. Rossignol dated 28 April 2005.

III. Claim 1 of the patent in suit reads as follows:

"1. Compound of the formula



with the symbol R_1 representing OH."

IV. The opposition sought revocation of the patent in suit in its entirety *inter alia* for lack of novelty or

inventive step. *Inter alia* the documents (1), (2) and (3) were cited in the opposition proceedings.

V. The Opposition Division held that the process of preparation of Nitazoxanide disclosed in document (2) did not refer to Tizoxanide, i.e. the compound of granted Claim 1, as an inevitable by-product resulting from the chemical reaction. The reaction product of the preparation example of document (2) was only the end product Nitazoxanide and any by-products in the reaction mixture were not regarded as implicitly disclosed therein.

Regarding inventive step, the Opposition Division held that the technical problem to be solved could be seen in the provision of compounds having a lower toxicity as compared to Nitazoxanide disclosed in document (2). The prior art cited did not give any hint to the person skilled in the art towards the claimed compound as a solution to the defined technical problem.

VI. Oral proceedings before the Board were held on 13 March 2007.

VII. The Appellant submitted for the first time with the statement of grounds of appeal that the claimed subject-matter was anticipated on the ground of prior use. Such an objection was supported by document (4).

VIII. The Appellant submitted in essence the following arguments:

The experimental report of F. Benigni, (document (3)), showed that in carrying out the process disclosed in

document (2) the skilled person would have inevitably arrived at a composition containing 1.34% Tizoxanide. Thus, there was an implicit disclosure of the compound of Claim 1, i.e. Tizoxanide.

Document (4) disclosed that Nitazoxanide was currently marketed in Europe by Institut Merieux under the trade name of Taenitaz for the control of cestodes in dogs and cats. Nitazoxanide was a stable, crystalline powder of 98% purity. The compound was synthesized by Chimos Laboratories. Although this document did not identify the remaining 2% of the product, the experimental report of F. Benigni, (document (3)), showed that a purity of 98% indicated without doubt the presence of measurable Tizoxanide traces.

Regarding inventive step, starting from document (1) as the closest state of the art, the technical problem to be solved could only be seen in the provision of further compounds having an anti-bacterial and anti-protozoa activity. In view of compound 26 disclosed therein, i.e. 2-(p-hydroxybenzoyl)amino-5-nitrothiazole, the person skilled in the art would have been directed to test the o-hydroxybenzoyl isomer, in particular because that document taught that substitution in the benzoyl moiety caused an increase of the activity. Thus, that document showed the strategy to be followed and led in an obvious manner to the claimed compound.

With a letter received on 2 August 2005, the Appellant requested the Board of Appeal to take further evidence under Article 117 EPC.

IX. The Respondent requested that the alleged public prior use and the evidence relied upon in support thereof be not admitted into the proceedings as late-filed and not highly relevant. In respect of the substantive issue of public prior use he submitted that the pharmaceutical product Taenitaz had never been marketed contrary to the statement of the authors of the document (4) as evidenced by document (5).

Furthermore, document (4) did not disclose that the remaining 2% of by-products contained Tizoxanide.

Regarding novelty over document (2), the skilled person without the knowledge of the present invention had no means to identify without undue burden Tizoxanide among the seven by-products formed during the process. There was, therefore, no implicit disclosure of Tizoxanide.

Regarding inventive step, the person skilled in the art would have noted from the whole teaching of document (1) that nonanoyl- and lauroyl substituents in 2-position were found to be the most active compounds whereas a benzoyl group resulted in decreased inhibition. Thus document (1) taught away from the instant invention. Furthermore, Tizoxanide had shown an anti-viral activity not suggested by document (1) and also a lower toxicity than well-known anti-parasitic agents such as Indomethacin, Nitazoxanide or Diclophenate. In that context, document (2) was more relevant than document (1) to the discussion of anti-parasital activity.

The Respondent also requested to reject the Appellant's requests under Article 117 EPC.

X. The Appellant requested that the decision under appeal be set aside and the patent be revoked.

The Respondent requested that the appeal be dismissed.

XI. At the end of the oral proceedings the decision of the Board was announced.

Reasons for the Decision

1. The appeal is admissible.

Novelty

2. Novelty of Claim 1 was first contested in view of the disclosure of document (2).

2.1 Document (2) discloses a process for preparing Nitazoxanide, i.e 2-(acetolyloxy)-N-(5-nitro-2-thiazolyl)benzamide, designated under the code number PH 5776. It was eventually conceded by the Appellant that such a document did not disclose explicitly that PH 5776 contained Tizoxanide. It was however argued that the process for preparing PH 5776 led **inevitably** to a mixture containing Tizoxanide as a by-product. In support of his contention, the Appellant submitted as evidence an experimental report of F. Benigni, (document (3)), allegedly showing that the synthesis of PH 5776 in the conditions disclosed in document (2), namely in the Examples (see column 2, lines 47 to 62), yielded a mixture of 75.1% of Nitazoxanide and 1.34% of Tizoxanide. Those entities were identified by HPLC (High Pressure Liquid Chromatography).

2.2 According to the constant jurisprudence of the Boards of Appeal, the disclosure by description in a cited document of the starting substance as well as the reaction process is always prejudicial to novelty of the end-product because those data unalterably establish the end-product (T 12/81, OJ EPO 1982, 296, point 13). In the present case, the burden of proof is upon the Opponent (now Appellant) to establish that a person skilled in the art reproducing the process at issue would **inevitably** arrive at a composition containing Tizoxanide. Insofar as a party seeks to establish an inevitable result by carrying out a prior published example, which does not itself explicitly disclose the alleged invention, every detail of the prior art example must be duplicated, save for exceptional circumstances where it is not practicable, or not reasonable, to do so (see T 396/89 of 8 August 1991, point 4.5 and T 441/90 of 15 September 1992, point 4.8).

2.3 In comparing the disclosure of the process set out in the Examples part of document (2) with respect to the conditions described in the experimental report, (document (3)), the Board notes that several modifications have been introduced by F. Benigni, namely it is not indicated that the tetrahydrofuran used as solvent was anhydrous, whereas this feature is explicitly mentioned in document (2) (see column 2, line 51); a step of drying was omitted after precipitation of the crude product (see column 2, line 58); and it is not indicated with which material the crude product was washed, whereas document (2) states that the obtained precipitate after drying was

washed with water (see column 2, lines 58-59). The Appellant did not provide any explanation for such discrepancies.

Furthermore, it remains unclear how F. Benigni could identify Tizoxanide among the seven by-products appearing in the HPLC chromatogram. No spectroscopic data or elementary analysis were submitted with respect to the peak allegedly corresponding to Tizoxanide. Retention time cannot be in that respect a proper means of identification since it varied between the chromatograms set out in the report, namely 14.56 for the sample coded S-2484 and 17.4-17.5 for the other samples.

2.4 In the light of all the material before it, the Appellant has not discharged the burden of proof which rested upon him to show that a **valid repetition** of the process for preparing PH 5776 of document (2) would lead inevitably to a mixture containing the claimed product and the objection of lack of novelty under Article 54(1)(2) EPC based on this citation must, therefore, fail.

3. Novelty was also contested due to prior use in view of document (4). The Respondent requested the Board to reject this objection and the evidence in support thereof as late-filed. The question arises, therefore, whether or not this objection of prior use can be admitted into the appeal proceedings.

3.1 According to Article 114(2) EPC facts or evidence which are not submitted in due time may be disregarded. In the extensive jurisprudence relating to this issue the

Boards of Appeal have developed the principles that the exercise of their discretion should be governed by the relevance of the late-filed material to the case at hand, the circumstances which led to the late filing, and general procedural economy (see the Case Law of the Boards of Appeal of the EPO, 4th edition 2001, Section VI. F. Late submission, points 1 to 3, pages 324-331).

3.2 The public prior use objection and the evidence submitted in support thereof, i.e. document (4), was submitted by the Appellant for the first time with his grounds of appeal. The Appellant did not put forward any reason for not having filed such an objection earlier. In such a case the Boards of Appeal normally admit such material into the proceedings only if it is *prima facie* highly relevant in the sense that it is highly likely to prejudice the maintenance of the patent.

3.3 According to the established jurisprudence of the Boards of Appeal in order to properly substantiate a public prior use objection it is necessary to establish:

(a) the date on which the prior use occurred (the "when" question),
(b) exactly what was used (the "what" question), and
(c) the circumstances surrounding the prior use, i.e. where, how and by whom was the subject-matter made public through that use.

If one of these issues is not proved, the Appellant's prior public use case must fail. In this context the standard of proof to be applied is "beyond any reasonable doubt" (see T 782/92, point 2.2).

3.4 The Appellant argued public prior use upon the basis that document (4) indicated (a) that Nitazoxanide was from 1985 on marketed in Europe by Institut Merieux under the trade name of Taenitaz for the control of cestodes in dogs and cats (see left-hand column, Introduction) (this being the Appellant's answer to the question "**when**") and (b) that Nitazoxanide was a stable, crystalline powder of 98% purity which implied that the remaining 2% by-product was Tizoxanide as shown by the report of F. Benigni, (document (3), this being the Appellant's answer to the question **"what"**).

3.5 However, regarding the question "when", the Respondent strongly contested that any product had been marketed and submitted in support thereof an affidavit of J.F. Rossignol, (document (5)), the inventor of the patent in suit, asserting that the statements of the authors of document (4) on this issue were wrong. In such circumstances, the Board considers that the evidence submitted by the Appellant is clearly insufficient, especially in consideration of the fact that document (4) was published in 1985, nine years before the priority of the patent in suit, and that the Appellant was unable to submit any evidence showing that Taenitaz was a registered medicament with a marketing authorization.

3.6 Regarding the question "what", the Appellant's contentions are not substantiated in view of the conclusion of the Board concerning the experimental report of F. Benigni (document (3), see point 2 above).

3.7 Therefore, in view of the fact that the Appellant has not been able to convincingly answer the **what** and **when** questions, the Board does not consider the public prior use objection *prima facie* highly relevant. The Board does not admit, therefore, this late-filed prior use objection into the proceedings, in compliance with Article 114(2) EPC.

Inventive step

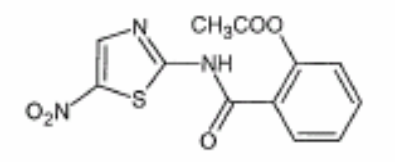
4. The subject-matter of Claim 1 relates to a chemical compound as such, i.e. Tizoxanide (see point III above). According to the patent in suit this compound may be used as anti-parasital, anti-bacterial, anti-fungal agent and anti-viral agent (see page 2, paragraph [0001] of the patent in suit). It was also indicated that by using the claimed compound even in very low amounts, it was possible to increase the efficiency of compound PH 5776, i.e. Nitazoxanide (see page 10, paragraph [0059] of the patent in suit).

5. According to the established jurisprudence of the Boards of Appeal it is necessary, in order to assess inventive step, to establish the closest state of the art, to determine in the light thereof the technical problem which the invention addresses and successfully solves, and to examine the obviousness of the claimed solution to this problem in view of the state of the art. This "problem-solution approach" ensures assessment of inventive step on an objective basis and avoids an ex post facto analysis.

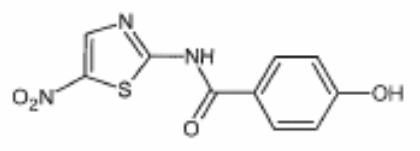
6. The first step is, therefore, to identify the closest state of the art. According to the established

jurisprudence of the Boards of Appeal the "closest state of the art" is normally a prior art document disclosing subject-matter aiming at the same objectives as the claimed invention and having the most relevant technical features in common, i.e. requiring the minimum of structural modifications (see the Case Law of the Boards of Appeal of the EPO, 4th edition 2001, Section I. D. 3.1., "Determination of the closest prior art", page 102).

6.1 Document (2) discloses as active parasiticidal, fungistatic and/or molluscicidal agent the compound having the code number PH 5776, i.e. 2-(acetolyloxy)-N-(5-nitro-2-thiazolyl)benzamide of formula



6.2 Document (1) discloses *in vitro* tests related to the inhibition of *Clostridium botulinum* by some 5-nitrothiazole derivatives among them compound No. 26, i.e. 2-(p-hydroxybenzoyl)amino-5-nitrothiazole of formula



the minimum inhibitory concentration (MIC) of which was 0.08μg/ml (see Table 1, page 354 of document (1)). An anti-protozoa action is suggested for these compounds via an anti-bacterial activity as these organisms (protozoa) cannot grow without the associated symbiotic bacteria (see page 355, right-hand column, second

paragraph of document (1)). Furthermore, this document indicates that the *in vitro* activity of 5-nitrothiazoles against *C. botulinum* was investigated for possible use as a nitrite substitute for inhibiting clostridia in cured meat products (see page 353, right-hand column, last full paragraph of document (1)).

6.3 Both documents (1) and (2) aim at the same objective as the patent in suit. Contrary to the Opposition Division, the Board considers that Document (1) is closer than document (2) because compound No. 26 of document (1) is a position isomer of Tizoxanide having, therefore, the same number and kind of atoms but having different bonding arrangements whereas PH 5776, i.e. Nitazoxanide, is a compound having a different functionality, namely an acetylated hydroxyl group. Compound No. 26 requires the minimum of structural modifications and document (1) is, therefore, the closest state of the art to define the technical problem to be solved.

7. Thus, starting from document (1), the technical results or effects successfully achieved by the claimed subject-matter are to be determined for defining the objective technical problem to be solved.

7.1 The Respondent relied upon the tests submitted to the Examining Division with the letter of 4 July 2001 showing that Tizoxanide revealed a lower toxicity than other well-known antiparasitic agents such as Nitazoxanide, Indomethacin and Diclofenac.

7.2 According to the established jurisprudence of the Boards of Appeal, some beneficial effects or advantageous properties, if appropriately demonstrated

by means of truly comparable results, can in certain circumstances properly form a basis for the definition of the problem that the claimed invention sets out to solve and can, in principle, be regarded as an indication of inventive step; the only comparative tests suitable for this are, however, those which are concerned with the **structurally closest state of the art to the invention**. The requirement for a comparison with the closest prior art is based on the principle of the structural dependence of the properties of chemical substances, i.e. on the fact that these properties reflect the structure of the substances. Given the similar properties to be expected in view of the structural similarity of two substances, evidence of an abrupt improvement can be regarded as unexpected. So if a meaningful statement is to be made in order to render an inventive step plausible, compounds having a maximum structural resemblance must be compared with one another (see T 181/82, OJ EPO 1984, 401, point 5 and T 955/96, point 5.10).

7.3 In the present case, the tests referred to by the Respondent do not establish a direct comparison between the claimed subject-matter and the technical matter disclosed in document (1) and for this reason are not relevant for defining the technical problem. Indeed, Nitazoxanide, Indomethacin and Diclofenac are not disclosed in document (1).

7.4 Since no beneficial effects or advantageous properties can be acknowledged vis-à-vis the closest state of the art, i.e. document (1), the technical problem in view thereof may only be viewed as the provision of further

5-nitrothiazole derivatives having anti-bacterial and anti-protozoa activity.

Having regard to the technical information provided in the patent in suit, in particular the *in vitro* test against *Trichomonas vaginalis* (see page 10, paragraph [0057] of the patent in suit), the Board considers it plausible that this technical problem has indeed been solved.

8. It remains to be decided whether or not the claimed solution is obvious in view of the prior art cited.

8.1 Document (1) discloses tests performed with a number of 5-nitrothiazoles derivatives with various substituents in the 2-position for inhibition of *Clostridium botulinum* (see general formula with R is NO_2 and the list of compounds, in Table 1, page 354). Document (1) aims to assess the influence of the substituent in the 2-position, i.e. "R", on the inhibition effect and this is measured by the minimum inhibitory concentration (MIC) in μg/ml. Document (1) also suggests that anti-protozoa activity could be expected given that those organisms could not grow without the associated symbiotic bacteria (see page 355, right-hand column, second paragraph).

Turning now to the results obtained, the more effective inhibition is observed with a 2-nonanoyl- and 2-lauroylamido- substituent (0.005 and 0.0025 μg/ml respectively) whereas a 2-benzoylamido group resulted in decreased inhibition (0.16 μg/ml)(see Table 1 and page 355, right-hand column, first paragraph of document (1)). Regarding the 2-benzoylamido

substituents, that document notes that 2-benzoyl- and 2-nicotinoylamido-5-nitrothiazole exhibited about the same activity as the unsaturated acyls (0.16 μg/ml). Substitution in the benzoyl moiety caused an increase of the activity. Thus 2-(p-chlorobenzoyl)amido- and 2-(p-hydroxybenzoyl)amido-5-nitrothiazole were twice as active as the benzoylamido-5-nitrothiazole compound itself (0.08 μg/ml)(document (1), Table 1 and right-hand column, "Results", page 355).

8.2 The Respondent argued that the person skilled in the art would have been deterred from investigating further 5-nitrothiazole derivatives having a benzoylamido moiety in the 2-position as a solution to the above defined technical problem since those compounds were much less active than the 5-nitrothiazoles having a nonanoyl or lauroylamido moiety in the 2-position (see point 8.1 above).

He also pointed out that the person skilled in the art in view of the anti-bacterial activity of the p-nitro benzoylamido substituent (MIC 0.01 μg/ml) versus the o-nitro benzoylamido substituent (MIC 0.04 μg/ml) would have been deterred from choosing an o-hydroxy benzoylamido substituent.

8.3 Obviousness is to be assessed in view of the technical problem to be solved. In the present case the technical problem to be solved is not to provide 5-nitrothiazole derivatives having **enhanced** anti-bacterial and anti-protozoa properties but merely **further** 5-nitrothiazole derivatives having anti-bacterial and anti-protozoa properties (see point 7.4 above). Only if the technical problem had been defined as an improvement, might the

Board have considered that the information contained in that document (1) could be viewed as a deterrent or as teaching away from the claimed subject-matter of the patent in suit.

8.4 Since this is not the case here, the question is whether the claimed compound is obvious in view of a prior art that discloses compounds having defined anti-bacterial and anti-protozoa properties.

8.5 The person skilled in the art, knows from document (1) that the 5-nitrothiazole having a benzoylamido substituent in 2-position, i.e. compound 23 of Table I, has an anti-bacterial activity against *Clostridium botulinum* which possibly gives rise to an anti-protozoa activity. He is also taught that substitution in the benzoyl moiety caused an increase of the activity, the compound 2-(p-hydroxybenzoyl)amino-5-nitrothiazole, i.e. compound 26 of Table I, being mentioned in that respect. In view of this teaching, the person skilled in the art would have been directed to vary the position of the hydroxyl substituent on the benzoyl group from the para-position to the ortho-position to get a compound having anti-bacterial and anti-protozoa activity. Thus, the person skilled in the art would have expected that the 2-(o-hydroxybenzoyl)amino-5-nitrothiazole would solve the above defined technical problem (see point 7.4 above) arriving, therefore, at the subject-matter of Claim 1 which for this reason is devoid of inventive step.

8.6 It does not matter in that respect that the claimed compound exhibits, in addition, an anti-viral activity since the compound is already obvious for the reasons

set out above and since claim 1 is not limited to this use.

8.7 Since the subject-matter of Claim 1 does not involve an inventive step in the sense of Article 56 EPC and since the Board can only decide on a request as a whole, the patent in suit is to be revoked.

9. *Requests for further evidence under Article 117 EPC*

9.1 In view of the outcome of the Appellant's appeal, there is no need for the Board to decide on the requests for taking further evidence.

As an *obiter dictum* the Board would nonetheless emphasise that the burden of proof for the alleged lack of patentability lies with the Appellant and cannot be dispensed with by requesting the Board, as the Appellant has done, to carry out its own investigations on the Nitazoxanide/Tizoxanide mixture, in particular, by summoning four named witnesses, by commissioning an independent expert to carry out experimental tests and by allowing individuals from the Appellant to attend any tests and to question witnesses or experts. Moreover, granting these requests would not be consistent with the character of the post-grant opposition proceedings under the EPC which are in principle to be considered as contentious proceedings between parties normally representing opposite interests, who should be given equally fair treatment (see G 9/91, OJ EPO 1993, 408, point 2). It is the responsibility of the Appellant to present the facts, evidence and arguments in support of the grounds on

which the opposition is based (see T 671/03 of 20 July 2006, point 2.1.1).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar The Chairman

N. Maslin A. Nuss