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Datasheet for the decision of 5 March 2014

Case Number: T 2244/11 - 3.3.01

Application Number: 04729974.8

Publication Number: 1740571

IPC: C07D401/12

Language of the proceedings: EN

Title of invention:
A PROCESS FOR PREPARING PYRIDINYLMETHYL-1H- BENZIMIDAZOLE COMPOUNDS IN ENANTIOMERICALLY ENRICHED FORM OR AS SINGLE ENANTIOMERS

Patent Proprietor:
Hetero Drugs Limited

Opponents:
Sagittarius Intellectual Property Consultants Ltd
Appelt, Christian W.

Headword:
Omeprazole enantiomers/HETERO DRUGS

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4), 13(1)

Keyword:
Admission of main request and auxiliary requests 1 and 3-6 (yes)
All requests: inventive step (no) - obvious modifications

Decisions cited:
T 0023/10, T 0144/09, T 1067/08, T 0936/09, T 0848/09, T 2485/11, T 0197/86, T 0234/03, T 0378/03

Catchword:

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Case Number: T 2244/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 5 March 2014

Appellant: (Patent Proprietor)	Hetero Drugs Limited Hetero House 8-3-166/7/1, Erragadda Hyderabad, Andhrapradesh. Hyderabad 500 018 (IN)
Representative:	Radkov, Stoyan Atanassov Urquhart-Dykes & Lord LLP The Podium 1 Eversholt Street London NW1 2DN (GB)
Respondent 1: (Opponent 1)	Sagittarius Intellectual Property Consultants Ltd Taylor House 39 High Street Marlow Buckinghamshire SL7 1AF (GB)
Representative:	Teuten, Andrew John Sagittarius IP Three Globeside Fieldhouse Lane Marlow, Buckinghamshire SL7 1HZ (GB)
Respondent 2: (Opponent 2)	Appelt, Christian W. Pettenkoferstrasse 20-22 80336 München (DE)
Representative:	Dormann, Holger Boehmert & Boehmert Pettenkoferstrasse 20-22 80336 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 8 August 2011 revoking European patent No. 1740571 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman:	A. Lindner
Members:	G. Seufert
	O. Loizou

Summary of Facts and Submissions

I. The patent proprietor lodged an appeal against the decision of the opposition division revoking European patent No. 1 740 571.

II. The present decision refers to the following documents:

(1) DE 40 35 455

(2) WO 94/27988

(3) Handbook of Reagents for Organic Synthesis, Chiral Reagents for Asymmetric Synthesis, John Wiley & Sons Ltd., Chichester (GB), 2003, pages vii to x and 176 to 178

(4) Aldrich Catalogue, Handbook of Fine Chemicals, 1999-2000, page 339

(5) Organic Synthesis, Collective Volume 5, John Wiley & Sons Inc., New York (US), 1973, pages 196 to 198

(6) C.-H. R. King *et al.*, Bioorganic & Medicinal Chemistry Letters, Vol. 10, 2000, pages 473 to 476

(7) CV Therapeutics, Inc., Drugs of the Future, Vol. 27, No. 9, 2002, pages 846 to 849

(8) K. Wiesner *et al.*, Canadian Journal of Chemistry, Vol. 50, 1972, pages 1925 to 1943

(9) J. Pfordt, Fresenius Z. Anal. Chem., 325, 1986, pages 625 to 626

(10) M. Hasan *et al.*, Tr. J. of Chemistry, 20, 1996, pages 228 to 233

(13) Encyclopedia of Reagents for Organic Synthesis, John Wiley & Sons Ltd. Chichester (GB), Vol. 2, 1995, pages 973 to 975,

(14) Reagents for Organic Synthesis, John Wiley & Sons, Inc., New York (US), 1967, page 109

(15) J. F. King, Canadian Journal of Chemistry,

Vol. 51, 1973, pages 3914 to 3922

(16) K. Nagarajan *et al.*, J. Indian Inst. Sci., 74, 1994, pages 247 to 255

(20) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., New York (US), 1994, pages v to viii, 297 to 299, 322 to 421, 1220

(20a) Basic Organic Stereochemistry, John Wiley & Sons, Inc., New York (US), 2001, pages, v to ix, 208 to 273 and 286 to 301

(21) P. Newman, Optical Resolution Procedures for Chemical Compounds, Vol. 1, "Amines and Related Compounds", Optical Resolution Information Center, Manhatten College, New York (US), 1978, pages ix, vii, 2, 3, section 1: pages 5, 7 to 24

(23) WO 01/14367

(24) English translation of document (1), submitted by the appellant during oral proceedings before the board

(25) "Comparison of reaction conditions for examples of D1 and of EP1740571B1", submitted by the appellant at the oral proceedings before the board

III. Notices of opposition were filed by opponents 1 and 2 (respondents 1 and 2) requesting revocation of the patent in suit in its entirety on the grounds of lack of inventive step and insufficiency of disclosure (Article 100(a) and (b) EPC). Opponent 1 additionally requested revocation of the patent in suit on the ground of added subject-matter (Article 100(c) EPC). With letter dated 13 May 2011, opponent 2 introduced lack of novelty as a new ground for opposition.

IV. The decision of the opposition division was based on a main request (claims as granted) and first to third auxiliary requests filed with letter of 13 May 2011.

The opposition division held that
- the main request contravened Article 123(2) EPC,
- the subject-matter of the first auxiliary request was insufficiently disclosed
- the second and third auxiliary requests lacked inventive step over document (1), taking into account the fact that camphorsulfonyl chloride was a well-known chiral auxiliary agent.

V. With the statement of grounds of appeal, the appellant filed a main request and auxiliary requests 1 to 4. The main request and auxiliary request 4 were identical to the second and third auxiliary requests underlying the contested decision. The appellant also filed documents (20) and (21).

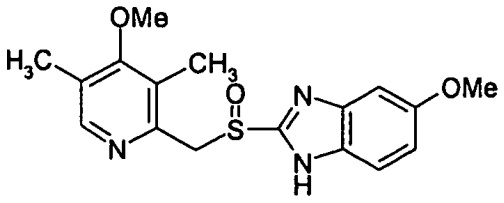
VI. Summons to oral proceedings were issued by the board on 4 December 2013.

VII. With letter of 13 January 2014, respondent 1 withdrew its request for oral proceedings.

VIII. With letter dated 4 February 2014, the appellant filed a new main request and auxiliary request 1. The previous main and auxiliary requests 1 to 4 were maintained as auxiliary requests 2 to 6. In addition, the appellant filed document (20a).

Independent claims 1 and 14 of the main request read as follows:

"1. A process for preparation of sulfoxide of formula I(i) as enantiomers or enantiomerically enriched enantiomers or a salt thereof:



---------- I(i)

which process comprises:

a) reacting a mixture of enantiomers of 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole or a salt thereof with (S)-camphor sulfonyl chloride to obtain diastereomeric mixture of 1-(S)-camphorsulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole and 1-(S)-camphorsulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole;

b) separating the diastereomers formed in step (a) by fractional crystallization; and

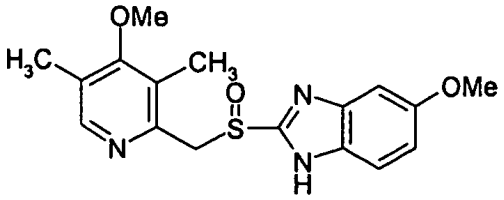
c) deprotecting the separated diastereomers with a base to provide a single enantiomer or enantiomerically enriched compound of (R)- or (S)-5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazole ((R)- or (S)-esomeprazole) and optionally converting the (R)- or (S)-esomeprazole to the salt."

"14. A compound selected from 1-(S)-camphorsulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole and 1-(S)-camphorsulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole."

Auxiliary request 1 differs from the main request in that compound claims 14 and 15 have been deleted.

Auxiliary request 2 consists of 17 claims. Independent claim 1 reads as follows:

"1. A process for preparation of sulfoxide of formula I(i) as enantiomers or enantiomerically enriched enantiomers or a salt thereof:



---------- I(i)

which process comprises:

a) reacting a mixture of enantiomers of 5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl) methylsulfinyl]-1H-benzimidazole or a salt thereof with (S) or (R)-camphor sulfonyl chloride to obtain diastereomeric mixture of 1-(S)-camphorsulfonyl-5-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole and 1-(S)-camphorsulfonyl-6-methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-(R/S)-sulfinyl]-1H-benzimidazole;
b) separating the diastereomers formed in step (a) and
c) deprotecting the separated diastereomers with an acid or a base to provide a single enantiomer or enantiomerically enriched compound of (R)- or (S)-5-Methoxy-2-[(3,5-dimethyl-4-methoxy-2-pyridyl) methyl-sulfinyl]-1H-benzimidazole ((R)- or (S)-esomeprazole) and optionally converting the (R)- or (S)-esomeprazole to the salt."

Independent claim 16 is identical to independent claim 14 of the main request.

Auxiliary request 3 differs from auxiliary request 2 in that deprotection with an acid has been deleted from step c).

Auxiliary request 4 differs from auxiliary request 2 in that the separation in step b) has been limited to fractional crystallisation. As a consequence, the claim corresponding to claim 8 of auxiliary request 2 has been deleted and the subsequent claims have been renumbered.

Auxiliary request 5 is a combination of auxiliary requests 3 and 4, i.e. step b) has been limited to fractional crystallisation and in step c) the deprotection with an acid has been deleted.

Auxiliary request 6 differs from auxiliary request 2 in that compound claims 16 and 17 have been deleted.

IX. With letter dated 27 February 2014, respondent 2 filed additional arguments based on document (23). A copy of document (23) was submitted by fax on 3 March 2014.

X. The appellant's arguments with respect to the decisive issues can be summarised as follows:

- Admission of the main request and auxiliary requests 1 and 3 to 6

The filing of further requests, if appropriate, was not excluded in appeal proceedings. The requests filed with the statement of grounds of appeal were rather limited in scope and provided no additional burden for the respondents. Concerning the newly filed main request and auxiliary request 1, they were provided reasonably in advance of the oral proceedings. They were based on

auxiliary request 3 provided with the statement of grounds of appeal (now auxiliary request 5, annotation by the board), contained no new subject-matter, were not difficult to understand and should simplify the discussion.

- Claim interpretation

The interpretation of claim 1 of the main request by respondent 2, in particular the alleged presence of chromatographic separation steps, was incorrect. The claim was limited to fractional crystallisation. Nothing else was intended or reflected in the wording of claim 1.

- Inventive step

Document (1) represented the closest prior art teaching the reaction of benzimidazoles with particular chiral auxiliary agents (see page 3, lines 24 to 39) to yield two pairs of diastereomers followed by chromatographic separation of isomers before separating the diastereomers by several crystallisation steps. The desired enantiomer was then liberated by solvolysis under strong acidic conditions. Fenchyl chloromethyl ether was the only chiral auxiliary agent proven to bind to benzimidazole nitrogen. No other type of chiral auxiliary agent was contemplated, nor was it certain how chemically different chiral auxiliary agents would perform in the process of document (1). The presently claimed process differed from the closest prior art in that camphorsulfonyl chloride was used as chiral auxiliary agent, the diastereomers were separated by fractional crystallisation, thereby avoiding chromatographic techniques, deprotection was carried out with a base, thereby avoiding the use of strongly

acidic conditions, and higher yields of S-omeprazole rather than low yields of R-omeprazole were obtained. These differences as a whole resulted in surprising and unexpected technical effects, i.e. lower costs, higher production efficiency and improved yields of the desired enantiomer, which were the consequence of a combined contribution of more than one of the technical features, as can be seen by comparing examples 5 and 6 of document (1) with examples 1 to 3 of the patent in suit. Accordingly, the problem to be solved was not merely the provision of an alternative process, but the provision of a "superior commercially viable process for producing omeprazole of the desirable configuration, i.e. S-omeprazole, the process having lower costs but at the same time higher efficiency and greater product yields".

The proposed solution was not obvious in view of common general knowledge. In this context, reference was made to documents (20) and (21), which showed that camphorsulfonyl chloride was neither a representative nor a favoured chiral auxiliary agent and therefore could not provide the skilled person with an incentive to modify the process of document (1), bearing in mind the technical problem to be solved. Document (1) itself provided no motivation to use chiral auxiliary agents of a different chemical type compared to those explicitly referred to in that document. Moreover, there was also no realistic expectation that using fractional crystallisation would have separated the desired (S)-omeprazole. Furthermore, none of the documents (3) to (5) and (13) to (15) provided the skilled person with an indication that the technical problem could be solved by using camphorsulfonyl chloride as chiral auxiliary agent and removing the camphorsulfonyl residue with a base. The same applied

with respect to documents (6) to (9), which were concerned with the optical resolution of structurally rather different amines. Concerning the basic deprotection conditions, even if the skilled person, in view of the disclosure of documents (2) or (6), had considered such conditions, he still would not have arrived at the claimed subject-matter because both documents relied on the separation of the diastereomers by chromatographic techniques. Moreover, document (6) clearly taught that fractional crystallisation of the diastereomers failed. In addition, the low yields resulting from the reaction of the amine with camphorsulfonyl chloride disclosed in documents (6) and (10) would have deterred the skilled person from using that particular auxiliary agent, in particular bearing in mind the technical problem to be solved.

The arguments with regard to the subject-matter of the auxiliary requests were essentially the same as those for the main request, although it was acknowledged that no data demonstrating improvements in yields were provided for a process using acidic deprotecting.

XI. The respondents' arguments with regard to the decisive issues can be summarised as follows:

- Admission of the main request and auxiliary requests 1 and 3 to 6

According to the respondents the main request and auxiliary requests 3 to 6 should not be admitted pursuant to Article 12(4) and 13(1) of the Rules of Procedure of the Boards of Appeal (RPBA). These requests could have been filed before the department of first instance. Moreover, the use of a base as compared with the use of an acid or a base was a new aspect

which had not been argued before the opposition division and was therefore not compatible with the nature of the appeal proceedings. The new main request and auxiliary request 1 had been filed very late in the proceedings together with a novel argument concerning an alleged synergistic effect. Their filing deprived the respondents of the possibility to have the claims considered by two instances.

- Claim interpretation

The appellant's depiction of the "present invention" was not reflected in the wording of claim 1 of the main request. Claim 1, due to the use of the word "comprises", included other separation steps besides fractional crystallisation. Furthermore, the alleged separation of a mixture of the (S)-sulfinyl 5-methoxy and (S)-sulfinyl 6-methoxy isomers was not reflected in claim 1, which merely referred to "separating the diastereomers formed in step (a)" without any indication as to which diastereomers were in fact separated. If the board concurred with the appellant that this feature was reflected in the wording of the claims, then the claimed subject-matter gave rise to an objection of insufficient disclosure.

- Inventive step

Document (1) was considered to represent the closest prior art teaching the use of chiral auxiliary agents Rchi-X for the separation of enantiomers of benzimidazoles, including omeprazole. Document (1) was not limited to the use of the specifically exemplified chiral auxiliary agents on page 3, lines 24 to 39, nor to the use of chiral auxiliary agents whose residue Rchi had to be removed under strongly acidic

conditions. It was sufficient that this residue could be removed smoothly. There were no doubts that camphorsulfonyl chloride reacted with the nitrogen atom of the benzimidazole and could therefore be used in the process of document (1). This was also confirmed by document (10). Fractional crystallisation for the separation of diastereomers was already part of the disclosure of document (1) (examples 1, 3 and 5 and page 3, lines 62 to 64) and therefore could not be considered as a distinguishing feature. Furthermore, the chromatographic separation of isomers disclosed in document (1) was not a mandatory step. Moreover, such a step was not excluded by the wording of claim 1 of the main request. The presently claimed process, therefore, differed from the process of document (1) merely in the use of camphorsulfonyl chloride in step a) and the use of a base in the deprotection step c). No technical effects had been shown to be associated with these distinguishing features. The problem to be solved was therefore the provision of an alternative process for producing enantiomerically pure or enriched (R)- or (S)-omeprazole. The appellant's comparison between examples 5 and 6 of document (1) and examples 1 to 3 of the patent in suit was inadequate as evidence of the alleged improvements, because the examples of the prior art and those of the patent differed in more than only the distinguishing features. Since no synergy or common effect were observed for the two distinguishing features, they could be treated independently. The use of camphorsulfonyl chloride as chiral auxiliary agent for amines was common general knowledge at the relevant date of the patent in suit, as exemplified in any of the documents (3), (5) to (10) and (13) to (16). This fact could not be put into question by documents (20) and (21) submitted by the appellant as evidence that this agent was neither a representative nor a favoured

chiral auxiliary agent. Its use in the process of document (1) was therefore an obvious alternative for the skilled person. Deprotection of the camphorsulfonyl residue was known to occur under acidic as well as basic conditions. Furthermore, document (1) already encouraged the skilled person to consider deprotection methods that relied on other than strongly acidic deprotection conditions by indicating that all chiral residues which can be smoothly removed were in principle suitable und that benzimidazoles were acid-sensitive compounds. Its stability under basic conditions was taught in document (2).

The arguments with respect to the auxiliary requests were essentially the same as those for claim 1 of the main request. It was, however, pointed out that, according to appellant's admission, the presence of a base was needed for achieving the alleged improvements.

XII. The appellant requested that the decision of the opposition division be set aside and the patent be maintained on the basis of the main request or, alternatively, of auxiliary request 1, both filed on 4 February 2014 or, alternatively, on the basis of one of the auxiliary requests 2 to 6 filed as main request and auxiliary requests 1 to 4 with the statement of grounds of appeal.

XIII. The respondents requested that the appeal be dismissed.

XIV. At the end of the oral proceedings, which took place as scheduled on 5 March 2014, the decision of the board was announced.

Reasons for the Decision

1. The appeal is admissible.

2. Admission of main request, auxiliary request 1 and auxiliary requests 3 to 6

2.1 Respondent 1 objected to the admission of auxiliary requests 3 to 5 under Article 12(4) RPBA and cited decisions T 23/10, T 144/09 and T 1067/08 in support of its arguments. At the oral proceedings before the board, respondent 2 raised the same objection and objections under Article 13(1) RPBA against admission of the main request and auxiliary requests 1 and 3 to 6.

2.2 According to Article 12(4) RPBA the board has the discretionary power to hold inadmissible facts, evidence or requests which could have been presented or were not admitted in the first-instance proceedings. When exercising their discretion the boards of appeal have to consider the specific circumstances of the case, bearing in mind that the purpose of an appeal is to offer the losing party the possibility to challenge the decision of the opposition division on its merits, and not to conduct the case anew.

This means that if new submissions are not precluded, their admission is restricted (T 23/10, point 2.2 of the Reasons, T 936/09, point 2 of the Reasons). According to established jurisprudence, amendments, including amended requests, which can be considered as a normal reaction of a losing party given the circumstance are usually allowed into the appeal

proceedings by the boards (T 848/09, point 1 of the Reasons; T 2485/11 point 2 of the Reasons).

2.3 In the cases cited by respondent 1 where new requests were not admitted under Article 12(4) RPBA the circumstances were different.

In decision T 144/09 the patent proprietor was informed at the oral proceedings before the opposition division that the introduction of a particular feature contravened Article 123(2) EPC. It made a "considered and deliberate choice" not to file any requests in an attempt to overcome this objection despite an invitation to do so by the chairman of the opposition division. With the statement of grounds of appeal the patent proprietor filed several sets of claims involving the deletion of the feature objected to by the opposition division. The board considered that claims with such a simple and straightforward amendment could and should have been filed before the department of first instance, at least in the form of auxiliary requests, and therefore declined to admit them. In decision T 23/10 the situation was similar.

In decision T 1067/08 the board did not admit a request, which the opposition division, in correct exercise of its discretion, had not admitted. The board considered that given the history of the claims their admission would be contrary to the judicial nature of the appeal proceedings and would render pointless the opposition division's correct decision not to admit them.

2.4 In the present case, auxiliary requests 3 to 5 were filed at the earliest possible stage in the appeal proceedings, namely with the statement of grounds of

appeal in direct reply to the opposition division's decision revoking the patent. They represent further limitations to the second auxiliary request underlying the contested decision, which the opposition division considered as not to involve an inventive step and which the appellant presently defends as its main request. They are not considered to represent a significant deviation from the line of defence followed during the opposition proceedings, thereby rendering the contested decision pointless or requiring the board to conduct the case completely anew, but are a legitimate attempt by the appellant to defend its patent in a more restricted form. Even if, theoretically, the appellant might have been able to file auxiliary requests 3 to 5 at the end of the oral proceedings before the opposition division, it is not apparent to the board that in the present case, unlike in T 144/09 or T 23/10, it deliberately withheld these requests. Rather, the formulation of a suitable request which would have overcome the opposition division's inventive step objection was not so immediately evident as in T 144/09 or T 23/10. Hence, given the circumstances of the case, the appellant's auxiliary requests 3 to 5 filed with the statement of grounds of appeal are considered to be a legitimate reaction of a losing party.

Concerning auxiliary request 6, the board observes that it is identical to auxiliary request 3 of the contested decision. Respondent 2's objection against this request under Article 12(4) RPBA is thus not justified.

2.5 Concerning the main request and auxiliary request 1, they were filed after the statement of grounds of appeal and after oral proceedings had been arranged. In accordance with Article 114(2) EPC and

Article 13(1) RPBA, admission of these request is at the board's discretion. The discretion is exercised in view of, *inter alia*, the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy. Amendments which require adjournement of the oral proceedings are usually not admitted (Article 13(3) RPBA).

2.6 In the present case, the board notes that the new main request is almost identical to auxiliary request 3 (now auxiliary request 5) filed with the statement of grounds of appeal. The only differences are that claim 6 and the expression "(R)-camphor sulfonyl chloride" in claim 1 have been deleted. These simple amendments - the latter may even be considered as an attempt to address an objection under Article 83 EPC raised by respondent 2 - neither increase the complexity of the case nor give rise to procedural complication preventing the discussion of this request during the oral proceedings before the board. The same applies to auxiliary request 1, which differs from the main request merely in that claims 14 and 15 directed to particular intermediates have been deleted.

With respect to respondent 2's argument that it was deprived of the possibility to present its case before two instances, the board notes that in proceedings before the EPO there is no absolute right for a party to have every aspect of a case examined by two instances. Other criteria, for example the general interest that proceedings are brought to a close, have equally to be taken into account. Moreover, neither respondent 2 nor respondent 1 had requested remittal to the department of first instance should the board decide to admit any of these requests.

2.7 For the aforementioned reasons, the board decided to admit the main request and auxiliary requests 1 and 3 to 6 into the proceedings.

3. Admission of documents (20a), (23) and (25)

3.1 Document (25) was submitted by the appellant during the oral proceedings before the board. It again compares examples 5 and 6 of document (1) - the document considered to represent the closest prior art in the decision under appeal - with examples 1 to 3 of the patent in suit - a comparison which the appellant already relied on during the written proceedings. It does not confront the respondents or the board with any new facts or evidence. Hence, the board, despite the absence of respondent 1, sees no reason to disregard it. Its admission was not objected to by respondent 2.

3.2 In view of the outcome (see point 7 below), it was not necessary for the board to decide on the admission of document (20a), presenting the same information as document (20), or document (23), submitted as alternative starting point for the assessment of inventive step.

Main request and auxiliary request 1 (filed with letter of 4 February 2014)

4. Amendments

4.1 Claim 1 of the main request finds its basis in original claim 48. The limitation to fractional crystallisation in step b) is disclosed in original claim 57 and on page 10, lines 12 to 14, of the application as originally filed. The limitation to the base in step c) finds its basis on page 11, line 13. Claims 14 and 15

have their basis in original claim 66 in combination with the scheme on page 13 of the description as originally filed. The amended claims therefore comply with Article 123(2) EPC. This was no longer contested by respondent 2, who declared at the oral proceedings before the board that it had no objections under this article. Respondent 1 had not raised any objections in this respect in the written proceedings.

4.2 The amendments restrict the scope of the claims as granted and therefore comply with Article 123(3) EPC. The respondents had no objections in this respect.

5. Invention as claimed

5.1 Before examining the objection of lack of inventive step, the board considers it appropriate to give its view on the proper technical understanding of the subject-matter of claim 1 of the main request.

5.2 Claim 1 relates to a process for the preparation of (R)- or (S)-omeprazole as a single enantiomer or in enantiomerically enriched form. Since claim 1 defines the process as "**comprising**" steps (a) to (c), the claimed subject-matter is not restricted to a process consisting of only these three steps, but may comprise further steps, either before step (a), after step (c) or even between each of the steps a) and b) or (b) and c), provided that the "in between" steps are technically meaningful and feasible. Further separation and/or purification steps are such technically meaningful and feasible steps and are therefore not excluded.

5.3 Furthermore, step (a) of the claimed process yields a diastereomeric mixture of two pairs of diastereomers,

namely 1-**(S)**-camphorsulfonyl-**5-methoxy**-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-**(R/S)**-sulfinyl]-1H-benzimidazole (i.e. diastereomeric pair A) and 1-**(S)**-camphorsulfonyl-**6-methoxy**-2-[(3,5-dimethyl-4-methoxy-2-pyridyl)methyl-**(R/S)**-sulfinyl]-1H-benzimidazole (diastereomeric pair B). According to step (b) the diastereomers formed in step (a) are separated by fractional crystallisation. There is, however, no indication as to which diastereomers are separated. Contrary to the appellant's view, the claimed subject-matter is therefore not limited to the subject-matter illustrated on page 10 of the patent in suit or in Annex 1 of the appellant's letter of 4 February 2014, which shows the simultaneous separation of the (S)-sulfinyl form of diastereomeric pair A and the (S)-sulfinyl form of diastereomeric pair B from the corresponding (R)-sulfinyl forms. The wording of claim 1 also encompasses a process where stereoisomeric pairs A and B are separated before separating the diastereomers by fractional crystallisation.

6. Insufficiency of disclosure

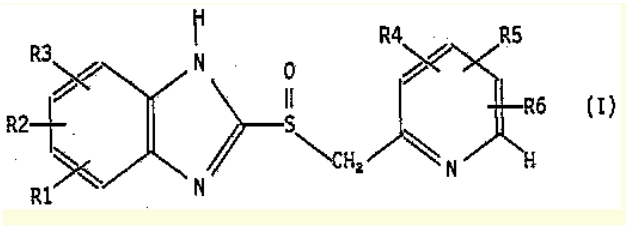
Given the understanding of the claimed subject-matter as explained in point 5 above, respondent 2 had no objections with respect to sufficiency of disclosure. Respondent 1 did not raise any objections in its written submission. Nor does the board see any reason to raise such an objection. Hence, it is not necessary to go into further detail in this respect.

7. Inventive step

7.1 Claim 1 of the main request is directed to a process for the preparation of omeprazole as a single enantiomer or in enantiomerically enriched form

comprising the reaction of an enantiomeric mixture of omeprazole with a chiral auxiliary agent, namely (S)-camphorsulfonyl chloride, separation of the diastereomers formed by fractional crystallisation and subsequent removal of the chiral auxiliary agent residue.

7.2 Formation and separation of diastereomers using chiral auxiliary agents followed by the removal of the chiral auxiliary agent residue is, indisputably, a well-known technique for the preparation of single enantiomers and belongs to the basic knowledge of a person skilled in the art. Moreover, such a process is already known in the state in the art for the preparation of enantiomers of omeprazole. Document (1) describes the preparation of enantiomers of compound (I), including omeprazole,



via the reaction of a racemate (i.e. a particular enantiomeric mixture) of compound (I) with a chiral auxiliary agent Rchi-X, separation of the diastereomers followed by deprotection under strongly acidic conditions to remove the chiral auxiliary agent residue and obtain a single enantiomer (see page 2, lines 28 to 68). Suitable agents Rchi-X are all chiral configuratively uniform compounds, which are able to react with compound (I) or its anion, and the radical "Rchi" of which can be removed smoothly and without undesirable side-reactions (page 3, lines 15 to 18). Separation of the diastereomers takes place according to known methods, preferably via fractional

crystallisation (page 3, penultimate paragraph). Isomers which are formed due to the prototropy of the benzimidazole may optionally be separated by chromatography before separating the diastereomers (page 3, line 65, to page 4, line 2). In examples 5 and 6, which were carried out according to examples 1 and 2, an enantiomer of omeprazole was prepared from racemic omeprazole sodium salt using (+)-fenchyl chloromethyl ether as chiral auxiliary agent. This reaction, due to the aforementioned prototropy, results in the formation of two pairs of diastereomers (i.e. the **(+)**-fenchyloxymethyl-**5-methoxy**-**(+/-)**-sulfinyl form (pair A) and the **(+)**-fenchyloxymethyl-**6-methoxy**-**(+/-)**-sulfinyl form (pair B)). The 5- and 6-methoxy stereoisomers were separated by chromatography (see example 1 and page 3, line 65, to page 4, line 2), the 5-methoxy-(+/-)-sulfinyl diastereomers were separated by fractional crystallisation and the isolated diastereomer deprotected with 90% sulfuric acid to obtain omeprazole in the form of a single enantiomer.

Thus, the board finds, in agreement with the opposition division and the parties, that document (1) represents the closest prior art and takes it as starting point for assessment of inventive step.

7.3 In the light of document (1), the appellant considered the technical problem to be solved by the present invention as the provision of a "superior commercially viable process for producing omeprazole of the desirable configuration, i.e. (S)-omeprazole, the process having lower costs but at the same time higher efficiency and greater end-product yields".

7.4 As evidence that this problem has been successfully solved by the claimed process, the appellant relied on

a comparison between examples 5 and 6 of document (1) and examples 1 to 3 of the patent in suit, in particular as shown in document (25).

7.5 It is established jurisprudence of the boards of appeal that if comparative tests are chosen to demonstrate an inventive step on the basis of an improved effect, the nature of the comparison must be such that the alleged advantage or effect is convincingly shown to have its origin in the distinguishing feature or features of the invention compared with the closest prior art (see T 197/86, OJ 1989, 371, T 234/03, T 378/03). In the present case, the distinguishing features compared to the prior art are the use of camphor sulfonyl chloride as chiral auxiliary agent and its deprotection with a base. Fractional crystallisation of the diastereomers is already disclosed in document (1) (see point 7.2 above) and therefore does not constitute a distinguishing feature. As explained in point 5 above, the wording of claim 1 is not restricted to the separation of the (S)-sulfinyl form of diastereomer A and the (S)-sulfinyl form of diastereomer B. It also does not exclude the presence of an additional separation step between steps (a) and (b) as disclosed in document (1). The "unexpected higher (S)-omeprazole yields, rather than the low (R)-omeprazole yields" is not a distinguishing feature of the claimed process as argued by the appellant in its written submission, but rather the technical effect allegedly achieved by the claimed process. Moreover, claim 1 is not limited to the preparation of (S)-omeprazole, but refers to the preparation of one enantiomer or enantiomerically enriched form of omeprazole, which can be either (R)- or (S)-omeprazole (see point VIII above).

7.6 Considering document (25), it is immediately obvious that examples 1 to 3 of the patent in suit differ from examples 5 and 6 of document (1) in more than only the aforementioned distinguishing features. They also differ, for example, in the starting material (i.e. omeprazole vs omeprazole sodium salt), the solvent (dichloromethane and N,N-diisopropylethylamine vs N-methylpyrrolidone), the temperature (0 to 5°C vs 25 to 35°C), the molar ratio between starting material and chiral auxiliary agent and the batch size. Since each of these additional differences can readily affect the overall yield, it cannot be validly concluded that the improvement in overall yield relied on by the appellant has its origin in the distinguishing features, namely the use of camphorsulfonyl chloride as the chiral auxiliary agent and deprotection with a base. The same applies with respect to the alleged improvements in costs or production efficiency. The appellant's comparison is therefore inadequate to conclusively demonstrate any improvements over the prior art, let alone any "synergistic" effects as alleged by the appellant.

7.7 According to established jurisprudence of the boards of appeal, alleged but unsupported advantages cannot be considered in the determination of the technical problem underlying the invention. Consequently, the technical problem as defined by the appellant needs to be redefined in a less ambitious way, namely as the provision of a further process for the preparation of omeprazole as pure enantiomer or in enantiomerically enriched form.

In view of the examples provided in the patent in suit, the board is satisfied that this problem has been solved.

7.8 It then remains to be decided whether or not the proposed solution is obvious in view of the prior art.

7.8.1 Document (1) teaches that all chiral, configuratively uniform residues which can be derived from naturally occurring or synthetically accessible chiral compounds and which can be split off solvolytically under acidic conditions are suitable as residue Rchi (document (1), page 3, lines 22 to 24). The teaching of document (1) is not restricted to the particular residues cited on page 3, lines 25 to 33.

7.8.2 At the relevant date of the patent in suit camphorsulfonyl chloride, which falls under the general definition of the chiral auxiliary agent Rchi-X of document (1), was a well-known chiral auxiliary agent for the optical resolution of amines, i.e. their separation into enantiomers. This common general knowledge is reflected in documents (3), (5), (13) or (14), and its practical application is illustrated in documents (6), (7) or (9). It was not contested that camphorsulfonyl residue can be removed under strongly acidic conditions. This is confirmed by document (7) (see page 847, scheme 1). It is, however, also known in the art that the camphorsulfonyl residue can be readily removed under basic conditions (document (6), scheme 1). Hence, the use of camphorsulfonyl chloride as chiral auxiliary agent Rchi-X in the process of document (1) and the basic instead of acidic removal of the camphorsulfonyl residue are measures which do not go beyond routine modifications that a person skilled in the art seeking to provide a further process for the enantiomeric resolution of omeprazole would consider. Moreover, for a skilled person it is already apparent from document (1), which indicates that the

benzimidazoles are acid-sensitive compounds, that it may be worthwhile trying to avoid acidic conditions in the deprotection step if the chiral agent employed allows different conditions. This is confirmed by document (2), which, in view of the acid sensitivity of omeprazole (page 1, lines 26 to 30), taught the use of a chiral auxiliary agent which could be removed under basic conditions.

Furthermore, there was nothing submitted from which the board could reasonably conclude that the skilled person would have been advised not to consider the use of camphorsulfonyl chloride in the process of document (1). Document (1) teaches that all configuratively uniform agents Rchi-X able to react with the benzimidazoles of formula (I) are in principle suitable. In the absence of convincing evidence to the contrary, the board has no reason to doubt that the benzimidazoles of document (1), including omeprazole, will react, as expected, with camphorsulfonyl chloride to form a covalent bond with the nitrogen atom of the benzimidazole ring. Moreover, such a reaction is confirmed by document (10) (page 232, scheme 1).

7.8.3 During the oral proceedings before the board, the appellant did not dispute that there was a host of resolving agents at the disposal of a person skilled in the art and that the removal of camphor sulfonyl chloride with acid or base was known. Instead it relied on the presence of unexpected and surprising improvements, in particular considerable improvements in yield, achieved by the combined use of the claimed chiral auxiliary agent and its basic deprotection, which it considered as not being obvious with respect to the available prior art documents. However, this argument cannot succeed, since no such improvements

were properly demonstrated and the problem to be solved is merely the provision of a further process (see point 7.7 above).

7.8.4 The board also disagrees with the appellant's argument that the skilled person would not have considered the use of camphorsulfonyl chloride, because of the low yield in its reaction with the amine reported in documents (6) (page 473, right column, second paragraph) and (10) (table 1) and because document (6) allegedly taught that fractional crystallisation failed (page 473, left column, last paragraph).

Considerations with regard to potentially lower yields are irrelevant if the problem to be solved is merely the provision of a further process. Concerning the alleged failure to separate diastereomers by fractional crystallisation in document (6), the board notes that this failure is reported for the separation of diastereomeric **salts** formed by reaction of the amine with a variety of chiral acids. No conclusion can be drawn with regard to the behaviour of compounds where the chiral auxiliary agent is covalently attached. The board also notes that document (6) uses column chromatography for separation of the diastereomers formed with camphorsulfonyl chloride. However, this is not tantamount to a statement that fractional crystallisation of such diastereomers is impossible.

7.8.5 The board also disagrees with the appellant's attempt to disprove the fact that camphorsulfonyl chloride was a suitable chiral auxiliary agent for optical resolution of amines at the relevant date of the patent in suit, in particular by referring to documents (20) and (21).

Camphorsulfonyl chloride is, admittedly, not mentioned in the section "Resolving agent for basis" in document (20). However, document (20) does not claim to provide an exhaustive list of all suitable chiral auxiliary agents. On the contrary, document (20) states on page 329, 9 to 12: "No attempt has been made to present an exhaustive list of resolving agents from the large literature on resolution but the compounds whose structures are given are representative". What the authors of document (20) consider as representative is their subjective choice and cannot be used to disqualify the teaching of other textbooks like documents (3), (5), (13) or (14). Document (21) explicitly mentions camphorsulfonyl chloride as a chiral auxiliary agent suitable for the optical resolution of amines and related compounds. The appellant's argument that it was only one amongst a variety of other suitable chiral auxiliary agents and was not mentioned as being particularly favoured is not relevant in the present context, since the problem to be solved is merely the provision of a further process and requires nothing more than the selection amongst known chiral auxiliary agents suitable for the purpose. In these circumstances, there is no need for an additional pointer or a specific incentive.

7.9 For the aforementioned reasons, the board concludes that the subject-matter of claim 1 of the main request and, due to its identical wording, of claim 1 of auxiliary request 1 does not involve an inventive step (Article 56 EPC). These requests must therefore be refused.

Auxiliary requests 2 to 6 (filed with the statement of grounds of appeal)

8. The subject-matter of claim 1 of the main request also forms part of the subject-matter of claim 1 of auxiliary requests 2 to 6. Accordingly, the subject-matter of claim 1 of these requests lacks inventive step for the same reasons as claim 1 of the main request (points 7.8 and 7.9 above). Therefore, these requests must also be refused.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated