Internal distribution code:

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

Datasheet for the decision of 20 December 2018

Case Number: T 2192/13 - 3.3.02

Application Number: 12151962.3

Publication Number: 2540729

IPC: C07D513/04, A61K31/4365, A61P9/00

Language of the proceedings: EN

Title of invention:
(7aS, 2'S)-2-Oxoclopidogrel as anti-thrombotic compound

Applicant:
IPCA Laboratories Limited

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2192/13 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 20 December 2018

Appellant: (Applicant)	IPCA Laboratories Limited 48, Kandivali Industrial Estate Charkop Kandivali (West) 400 067 Mumbai, Maharashtra (IN)
Representative:	Rees, Kerry WP Thompson 138 Fetter Lane London EC4A 1BT (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 24 May 2013 refusing European patent application No. 12151962.3 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	P. O'Sullivan
	L. Bühler

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application 12 151 962.3.

II. The evidence on file during examination proceedings included:

D2: Kazui *et al.*, Drug Metabolism and Disposition, 2010, vol. 38, no. 1, pp 92-99.
D4: Hagihara *et al.*, Drug Metabolism and Disposition, 2009, vol. 37, no. 11, pp 2145-2152.
D9: Declaration of Dr Ashok Kumar dated 22 October 2012
D11: Dansette *et al.*, Chem. Res. Toxicol., 2012, 25, pp 348-356.

III. The decision was based on the main request (claims as originally filed) as the sole request.

According to the contested decision:

The sole ground for refusal was that the set of claims of the main request lacked inventive step. D2 was the closest prior art, and disclosed clopidogrel and its metabolic pathway, as well as the claimed compound having unspecified sterochemistry at carbon 7a (figure 1). The technical problem, the provision of a further antiplatelet drug with improved efficacy compared to clopidogrel, was considered solved in view of the examples of the application which demonstrated improved efficacy. The solution was obvious in view of the prior art, in particular since it was known from D2 that the active metabolite was formed from metabolic 2-oxo-

clopidogrel. It was therefore obvious to the skilled person to employ the latter as the therapeutic drug to be administered, thereby avoiding formation of the undesirable inactive clopidogrel acid metabolite of formula IV (infra). Furthermore, in view of the common general knowledge of the skilled person, it was not unexpected that one diastereomeric isomer was more active than the other.

IV. That decision was appealed by the applicant (hereinafter: appellant). With the statement setting out the grounds of appeal the appellant requested that the decision of the examining division be set aside and that the case be remitted for formal completion of the grant procedure on the basis of the set of claims forming the basis for the contested decision, or alternatively on the basis of a set of claims as first auxiliary request also filed therewith. Further evidence was also filed. A set of claims as second auxiliary request was submitted with the letter of 20 November 2018.

V. A communication of the board was sent in preparation for oral proceedings. Therein the board *inter alia* raised objections in particular with respect to clarity (Article 84 EPC), and identified *inter alia* D4 as an appropriate starting point for the assessment of inventive step.

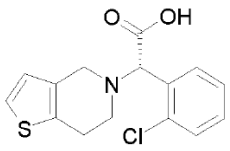
VI. During oral proceedings held on 20 December 2018, the appellant filed a set of claims 1-8 as new main request. All previously pending requests were withdrawn.

The independent claims of the main request read as follows:

"*1.Isolated methyl (7aS,2'S)-2-chlorophenyl)-2-(2,4,5,6,7,7a-hexahydrothieno[3,2-c]-5-pyridin-2-one)acetate isomer or its salts, solvates or complexes.*

3. A pharmaceutical composition comprising isolated methyl (7aS,2'S)-2-chlorophenyl)-2-(2,4,5,6,7,7a-hexahydrothieno[3,2-c]-5-pyridin-2-one)acetate isomer or its pharmaceutically acceptable salts(s).

8. The compound of claim 1 or 2, or the pharmaceutical composition of claim 3 to 7, for use:
in the treatment and / or prophylaxis of thrombosis and / or embolisms in a patient in need of such treatment, while avoiding and/or alleviating the side effects associated with the clopidogrel metabolites at least of Formula IV,



Formula IV

comprising administering an effective amount of the compound of Claim 1 or 2, or the pharmaceutical composition of claim 3 to 7."

VII. The appellant's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request - inventive step (Article 56 EPC)

(a) D2 was the closest prior art since it disclosed clopidogrel and its metabolic pathway. Claim 1

differed from the disclosure in D2 in that the known metabolite 2-oxo-clopidogrel was provided as the therapeutic drug to be administered in the form of the specific (7aS, 2'S) diastereomer. The technical problem was the provision of a further anti-thrombotic drug with improved efficacy compared to clopidogrel.

(b) The skilled person would not be led to the subject-matter of claim 1 in order to solve this problem, *inter alia* for the following reasons. Firstly, none of the prior art suggests that 2-oxo clopidogrel could or should be used as an active pharmaceutical ingredient in its own right, the prior art merely identifying it as a non-active metabolite. The skilled person would have looked to the active thiol metabolites disclosed in the prior art as a starting point towards solving the technical problem.

(c) Secondly, the chemical nature of 2-oxo-clopidogrel would not motivate the skilled person to attempt to resolve its diastereomers at position 7a due to an expected loss of chirality through tautomeric interconversion attributable to the presence of three potential interconvertible isomers of formula II, VI and VII (infra). Since two of those isomers led to the loss of the chiral centre at the 7a carbon, equilibration to a diasteroemeric mixture through transient conversion and dynamic equilibration would be expected. The presence of tautomerism was demonstrated in D11 and by the stability data provided in D9.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the claims of the main request filed during the oral proceedings of 20 December 2018.

Reasons for the Decision

1. Amendments (Article 123(2) EPC)

1.1 Claim 1 finds basis in claim 5 as originally filed, first alternative.

1.2 Claim 2 finds basis in claim 5 as originally filed, second to fourth alternatives. The dependency of claim 2 from claim 1 arises from the fact that said second to fourth alternatives fall within the scope of the first alternative.

1.3 Claims 3 to 7 find basis in originally filed claims 6 to 10 in combination with the second to fourth alternatives of claim 5 as originally filed. Originally filed combination claims 8-10, effectively dependent on the originally filed independent composition claim 6, were re-worded as composition claims; the previously implicit dependency was added explicitly.

1.4 Claim 8 finds basis in claim 11, first alternative, as originally filed.

1.5 It follows that the requirements of Article 123(2) EPC are met.

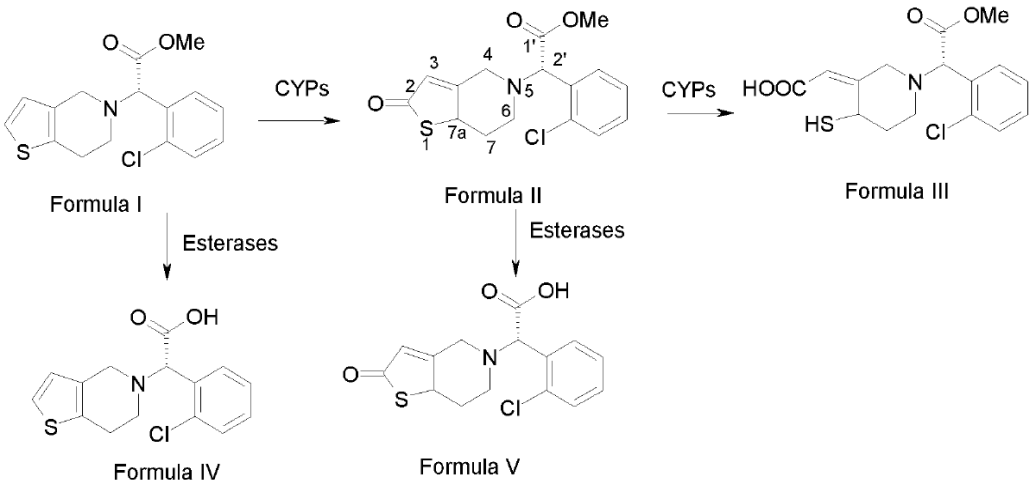
2. Clarity, sufficiency of disclosure and novelty (Articles 84, 83 and 54 EPC, respectively)

2.1 The board is satisfied that the claims according to the main request are clear, and that the invention described therein is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. The board additionally sees no reason to deviate from the conclusion of the examining division in the contested decision, which applies equally to the claims of the present main request, that the claimed subject-matter is novel.

3. Inventive step (Article 56 EPC)

Background

3.1 The metabolic pathway leading from the known therapeutic drug clopidogrel (formula I) to the therapeutically active metabolite (formula III) is known from the prior art (e.g. D4, figure 1) and is reproduced in the application (scheme 1):



3.2 Independent claim 1 is directed to the specific stereoisomer of the oxo-clopidogrel metabolite of Formula II having the configuration *S* at carbon 7a, its salts, solvates or complexes.

3.3 The present application aims at improving the efficacy of clopidogrel and ameliorating its limitations, which include slow onset of action, high inter-individual variability, poor metabolizer status and dose ceiling effect (paragraph [0017]).

4. Closest prior art

4.1 According to the decision under appeal, D2 represents the closest prior art. This view is shared by the appellant. While D2 is not unsuitable, the board is of the opinion that D4 represents a more appropriate starting points for the skilled person, since it more explicitly discloses the limitations and problems associated with the use of therapeutic clopidogrel and addressed in the present application. More specifically, in the same way as the present application, D4 (abstract) addresses the problem of clopidogrel having less efficiency and higher variability than its analogue prasugrel. On the contrary, D2 (abstract) aims at identifying the human cytochrome P450 isoforms involved in the two oxidative steps in the bioactivation of clopidogrel and does not focus on the problems addressed in the present application.

4.2 D4 concerns mechanistic studies undertaken with a view to elucidating the differences in efficiency and inter-individual variability of active metabolite formation/ bioactivation *in vivo* in prasugrel (a related anti-platelet drug) and clopidogrel. The metabolic pathway

for clopidogrel is depicted and both the active and inactive (acid) metabolites are identified (figure 1). In discussing the *in vitro* tests, the investigators concluded that clopidogrel was largely converted (figure 4: 92%) to an inactive acid metabolite (corresponding to Formula IV, supra) by hCE1, which competes with the oxidation of clopidogrel to form 2-oxo-clopidogrel (denoted "thiolactone metabolite" in figure 1). 2-Oxo-clopidogrel is then converted to the corresponding "clopidogrel active metabolite" (corresponding to Formula III, supra). It is stated that since a large inter-individual variability in hCE1 activity had been reported (elsewhere), the 2-oxo-clopidogrel formation level might change depending on individual hCE1 activities (page 2150, right hand column, "*To clarify the mechanism ...*"). To facilitate elucidation of the above reaction pathway, the 2-oxo-clopidogrel employed in D4 was synthesised by Daiichi Sankyo Co Ltd., Japan. This compound corresponds to the compound of claim 1 (see formula II, supra) with the exception that the configuration at the chiral ring junction (carbon 7a) was neither depicted nor discussed in D4. Indeed, the fact that a chiral centre exists at this carbon is not addressed in D4 at all.

5. Problem solved

5.1 According to the application as filed, the general object of the invention is to provide improved medications which overcome the limitations of clopidogrel, in particular its slow onset of action, high inter-individual variability, poor metabolizer status and dose ceiling effect as well as to increase its inhibitory capacity on ADP induced platelet aggregation (paragraph [0016]).

5.2 In order to formulate the objective technical problem effectively solved by the claimed subject-matter, it must be determined whether the distinguishing features of the claim over D4 provide the alleged technical effects or advantages.

Claim 1 differs from the disclosure in D4 in that:

- the known metabolite 2-oxo-clopidogrel was provided as the therapeutic drug to be administered; and

- specifically the (7aS, 2'S) diastereoisomer was provided, in contrast with the prior art in which stereoisomerism at the ring junction carbon 7a was neither identified nor discussed.

5.3 The preparation of the claimed compound (as the free base) as a diasteriomeric mixture is described in the application (paragraphs [0090] and [0091]) in a ratio of *S:R* (at carbon 7a) of 53.62:46.38, from which the desired 7a(*S*) isomer was crystallised in 60% yield (paragraphs [0092]-[0094]). The product was characterised by ^{1}H NMR (table 2) and had a ratio of 7a*S* to 7a*R* isomers of 99.5:0.5 (chiral HPLC). That the isolated compound was indeed the desired 7*a(S*) isomer was confirmed by single crystal data analysis (page 27, line 6). The corresponding hydrogen sulfate salt was crystallised from a mixture of 7a(*S)* and 7a(*R*) isomers in 93% yield and a ratio of chiral isomers of 99.8:0.2 (paragraphs [0097] and [0098]). A similar crystallisation was performed to yield the corresponding benzene sulfonate salt (paragraph [0102]).

5.4 The pharmacological tests demonstrated the effects arising from the above-mentioned differentiating features from the closest prior art. Thus the platelet aggregation tests (paragraphs [0107] - [0110]) demonstrate that the bisulphate salt of the compound of claim 1 provides for a higher level of inhibition of platelet aggregation (measured according to standard procedures, see paragraph [0105]) at a lower dose when compared to clopidogrel bisulphate. Thus while a 25 mg/kg dose of clopidogrel bisulphate led to a percentage inhibition of 77.15%, much lower doses of (7aS,2'S)-2-oxo-clopidogrel of 3.5 mg/kg and 2.5 mg/kg led to higher percentage inhibition of 90.86% and 85.43% respectively.

5.5 The anti-thrombotic tests (paragraphs [0111] - [0114]) also demonstrate that (7aS,2'S)-2-oxo-clopidogrel is at least comparable to clopidogrel bisulphate in the percentage inhibition of thrombus formation (76% and 73% respectively), but at a dose of approximately one third of that of the known drug (3.06 mg/kg versus 1.17 mg/kg of administered free base).

5.6 Additionally, it is demonstrated that (7aS,2'S)-2-oxoclopidogrel bisulfate, administered at a quantity of free base of 1.9 mg/kg was superior in percentage aggregation and inhibition to the corresponding diasteromeric mixture at carbon 7a, administered at a similar dosage (1.98 mg/kg free base; compare the last two entries of table 4).

5.7 Since there is no reason to suspect that other salts (other than bisulfite), solvates or complexes of the claimed compounds will not display a similar improved efficacy in solution, the tests sufficiently

demonstrate that the problem of improving efficacy has been solved over the entire scope.

5.8 The objective technical problem underlying claim 1 may consequently be formulated as the provision of a further anti-platelet drug with improved efficacy compared to clopidogrel.

6. Obviousness

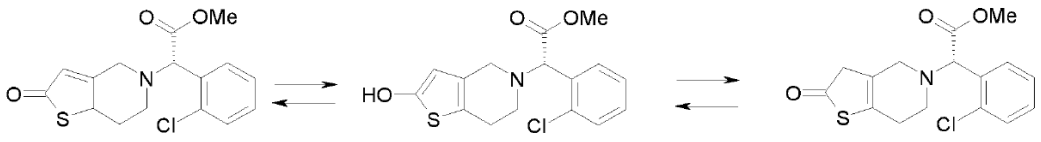
6.1 In order to solve the technical problem and arrive at the subject-matter of claim 1, the skilled person, in a first step, would be required to select the known 2-oxo-clopidogrel metabolite as the therapeutic drug to be administered, and in a second step, choose to (attempt to) isolate the claimed (7aS, 2'S) diastereomer.

6.2 In order to acknowledge inventive step of the subject-matter of claim 1, it would be sufficient to conclude that the skilled person, desiring to solve the above-mentioned problem, would not have implemented at least one of these steps.

6.3 Beginning with the second step, the board agrees with the view of the examining division set out in the contested decision that it is in general known to the person skilled in the art that in enantiomeric-, and by analogy, diastereomeric mixtures, one enantiomer or diastereomer is often more active than the other, and that thereby, generally speaking, the incentive exists for the skilled person to test the activity of each stereoisomer.

6.4 The appellant, both in the statement of grounds of appeal, as well as in the application itself

(paragraphs [0013] and [0014]) submits that the chemical nature of 2-oxo-clopidogrel (formula II, infra) would not motivate the skilled person to attempt to resolve its isomers due to an expected tautomeric inter-conversion. Thus, both from common general knowledge as well as from the evidence provided by the prior art, the skilled person would expect tautomeric inter-conversion at the chiral ring junction carbon 7a due to the presence of three potential interconvertible isomers of formula II, VI and VII (application, page 6):



Formula II Formula VI Formula VII

6.5 Since interconversion to two of those isomers (of Formula VI and VII) leads to the destruction of the chiral centre at the 7a position, racemisation at the 7a position through transient conversion and dynamic equilibration would be expected. The appellant submits that since the skilled person would also expect said interconversion *in vivo*, he would not attempt to resolve the isomers.

6.6 In response to this argument, the examining division in the contested decision concluded that there was no evidence for this assumption.

6.7 However, the board agrees with the position of the appellant, as set out in the following. It is basic chemical knowledge that in standard keto-enol tautomerism, the keto form, due to the bond energy of the C=O bond, is usually the most thermodynamically

stable, and the equilibrium will be expected to lie mostly on the side of the keto form (for example, in the case of acetone or acetaldehyde). However, one of the factors that can potentially shift this equilibrium towards the enol form is aromaticity. For example, although phenols exist in their keto forms, the enol form is favoured due to aromatic stabilisation. Analogously, the thiophene ring in the above structural enol (more specifically thiophen-2-ol) isomer of formula VI has aromatic character, as supported by the fact that thiophen-2-ol is a commercially available, and thus stable chemical compound. It follows that it is at least plausible that a certain amount of keto-enol tautomerisation will occur as argued by the appellant, and that consequently, the skilled person would expect any chirality at the 7a carbon to be at least labile.

6.8 In support of these theoretical considerations, the crystallisation examples of the application itself appear to demonstrate that isomerisation takes place in solution. Thus in the preparation of the free base starting from a mixture of chiral isomers in position 7a in an *S*:*R* ratio of 53.62:46.38, the yield of the desired chirally pure (99.5:0.5) crystalline *S*-isomer is 60% (52 g of the desired crystals; example 2 of the application). Since more of the crystalline *S*-isomer was isolated (60%) than was present in the starting material (53.62%), isomerisation at the 7a position must have occurred.

6.9 The same applies even more so to the preparation of the hydrogen sulfate salt according to which a 93% yield of crystalline (*S*)-isomer was obtained from an initial starting material *S*:*R* ratio of 51.42:47.48 (example 3 of the application).

6.10 Furthermore, although not available to the skilled person at the effective date of the application, D11, (published after the priority date) and the declaration of Dr Kumar (D9; unpublished) provide further indications that the above considerations are not flawed.

6.11 D11 demonstrates that the alleged tautomerisation indeed takes place in oxo-clopidogrel. In investigating the nature of various isomers of the active thiol metabolite produced in the bioactivation of clopidogrel, it was concluded that the existence of the 4b "endo" isomer (figure 2) could be attributed to the tautomeric equilibrium that could exist between 2b (oxo-clopidogrel) and the tautomer 2b', in which the double bond had migrated within the pyridine ring and was no longer conjugated with the keto group (D11, figure 5). The tautomer 2b' corresponds to the enol structure of formula VII, supra. The existence of this equilibration was indicated by the exchange of both the vinylic hydrogen (H3) and the allylic hydrogen (H7a) with CD_3OD in the presence of K_2CO_3, as shown by ^1H NMR and MS.

6.12 D9 also credibly demonstrates that the alleged tautomerisation of oxo-clopidogrel must indeed occur in solution. Sections 6-10 thereof report the attempted separation of the diastereomers at position 7a by chiral chromatography, which indicated that the isomers are well separated and thus chiral preparative HPLC initially appeared feasible. Eluted fractions were collected, by cutting individual peaks, but the result showed that each peak comprised more than 1 isomer, indicating that isomerisation in solution had occurred (section 7). The composition of the isomeric mixture

was studied over time, and indicated an equilibration (i.e. a loss of diastereomeric purity at carbon 7a) through tautomerism (D9, Exhibit 1, section 6 and section 7). Thus isolation of the diastereoisomers at the 7a position was not feasible by preparative HPLC.

6.13 In view of these considerations, the board concludes that with a view to solving the technical problem as formulated above, the skilled person, at least in said second step, would not have sought to separate the isomers at the 7a position to arrive at the subject-matter of claim 1.

6.14 Independently, but in addition to the above, the board notes that given the susceptibility of the claimed compound, as shown by D9 (supra), to equilibrate in solution from the desired pure 7a(*S)* isomer to the mixture of 7a(*S)* and 7a(*R)* isomers at carbon 7a, it could not have been predicted that *in vivo,* the metabolic processing of the (7a*S*) isomer would compete favourably with this equilibration. But in fact, the 7a(S) isomer is consumed *in vivo* at a faster rate than the rate of said equilibration. This is demonstrated in table 4 of the application (addressed under section 5.6, supra).

6.15 The claimed subject-matter is thus not obvious when starting from D4 as closest prior art.

Incidentally, it is noted that the same would apply even if the examining division's choice of D2 as the closest prior art were to be followed. More specifically, in the same way as for D4, D2 does not disclose the known metabolite 2-oxo-clopidogrel as the therapeutic drug to be administered, let alone its specific (7aS, 2'S) diastereoisomer. Hence, the

distinguishing feature would be the same when starting from D2 as the closest prior and the above considerations with regard to D4 would apply equally.

6.16 It follows that the subject-matter of claim 1 and claim 2 dependent thereon involves an inventive step. Claims 3-7 directed to a pharmaceutical composition comprising the compound of claim 1, as well as claim 8 directed to said compound or pharmaceutical composition for use in a method of treatment, equally involve an inventive step by analogy.

7. The set of claims 1-8 according to the main and sole request fulfills the requirements of the EPC and is consequently allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the examining division with the order to grant a patent with the following claims and a description to be adapted thereto:

claims 1 to 8 of the main request filed during oral proceedings on 20 December 2018.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated