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Datasheet for the decision of 19 July 2019

Case Number: T 0469/16 - 3.3.02

Application Number: 10754274.8

Publication Number: 2475676

IPC: C07J71/00, A61K31/58, A61P5/44

Language of the proceedings: EN

Title of invention:
Pregnane derivatives condensed in the 16,17 position with an N-substituted isoxazolidine ring as anti-inflammatory agents

Applicant:
Chiesi Farmaceutici S.p.A.

Headword:

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step

Decisions cited:

Catchword:

Europäisches Patentamt
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Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 0469/16 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 19 July 2019

Appellant: (Applicant)	Chiesi Farmaceutici S.p.A. Via Palermo, 26/A 43100 Parma (IT)
Representative:	Minoja, Fabrizio Bianchetti Bracco Minoja S.r.l. Via Plinio, 63 20129 Milano (IT)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 9 October 2015 refusing European patent application No. 10754274.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	M. O. Müller
Members:	A. Lenzen
	M. Blasi

Summary of Facts and Submissions

I. The appeal by the applicant (hereinafter: appellant) lies from the decision of the examining division to refuse its European patent application No. 10 754 274.8.

II. The decision of the examining division was based on a main request and an auxiliary request, the sets of claims of which were filed with the letter dated 10 June 2015 and during the oral proceedings on 18 September 2015, respectively. The claimed subject-matter of both requests was found to lack an inventive step.

III. Among the documents cited during the examination procedure, the following one is relevant to the present decision:

D1 "Synthesis and Topical Antiinflammatory Activity of Some Steroidal [16α,17α-*d*]Isoxazolidines", J. Med. Chem. 1982, 25, pages 1492 to 1495

With its letter dated 10 June 2015, the appellant had submitted comparative experimental tests (hereinafter: experimental evidence).

IV. With its statement of grounds of appeal, the appellant filed, *inter alia*, sets of claims of a main request and an auxiliary request, both of which were identical to those on which the impugned decision was based.

V. On 2 May 2019, the board issued a communication pursuant to Article 15(1) RPBA in which it raised objections under Articles 84 and 56 EPC.

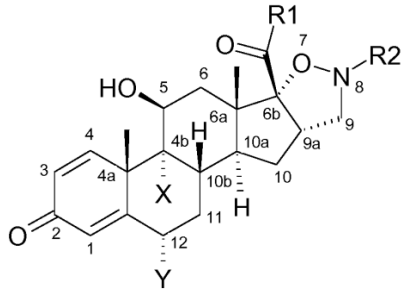
VI. By letter dated 30 May 2019, the appellant filed, *inter alia*, sets of claims of a new main request and a new auxiliary request.

VII. Oral proceedings before the board were held on 19 July 2019.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims of the main request or, in the alternative, of the auxiliary request, both as filed with its letter dated 30 May 2019.

IX. Independent claim 1 of the main request reads as follows:

"*A compound of general formula (I')*



(I')

wherein
R1 is $(CH_2)_n$-Z-$(CH_2)_{n'}$-R4 wherein n and n' are each independently 0, 1 or 2;
Z is a single bond or is selected from the group consisting of S, O, CO and NR3, wherein R3 is selected from the group consisting of H, straight or branched $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, $(C_3$-$C_8)$cycloalkyl, aryl, aryl$(C_1$-$C_6)$alkyl and heteroaryl, which are optionally substituted by CN;
R4 is selected from the group consisting of:
- *H, halogen, OH, SH, CN, NH_2;*

- *aryl(C_1-C_6)alkyl, (C_1-C_6)alkylsulfonyl, (C_1-C_6)alkylcarbonyl, (C_1-C_6)alkylcarboxyl, O(C_1-C_6)alkylcarboxyl, (C_1-C_6)alkylamide and (C_1-C_6)alkoxy, which are optionally substituted by oxo groups;*
- *(C_1-C_6)alkyl which may be optionally substituted by one or more substituents selected from the group consisting of halogen atoms, CN, OH, NH_2, NO_2, CF_3 and SH;*
- *(C_2-C_6)alkynyl;*
- *a mono-, bi- or tricyclic saturated or partially saturated or unsaturated ring, such as (C_3-C_8)cycloalkyl, aryl, (C_5-C_{10})heterocycloalkyl or heteroaryl, optionally substituted by one or more halogen atoms or oxo groups;*

R2 is the group

- *$(CH_2)_pR8$ wherein R8 is selected from the group consisting of halogen, oxo, CN, OH, NH_2, NO_2; (C_3-C_8)cycloalkyl, aryl and a saturated, partially saturated or unsaturated optionally fused ring such as (C_5-C_{10})heterocycloalkyl, which are optionally substituted by one or more substituents selected from the group consisting of halogen, CO, CN, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, (C_1-C_6)carboxyalkyl, (C_1-C_6)alkoxy, (C_1-C_6)haloalkoxy and (C_1-C_6)alkylsulfonyl;*

wherein p is 0 or an integer from 1 to 6 and and X and Y are both fluorine atoms

And wherein 4a is (S), 4b is (R), 5 is (S), 6a is (S), 6b is (R), 9a is (S), 10a is (S), 10b is (S) and 12 is (S)

and pharmaceutically acceptable salts thereof."

Claims 2 to 5 of the main request are dependent on claim 1.

The main request comprises five further independent claims, namely, claims 6 to 10. Claims 6 and 7 are directed at processes for the preparation of compounds which are in each case a subset of the compounds as defined in claim 1. Claim 8 is directed at a pharmaceutical composition comprising, *inter alia*, a compound as defined in claim 1. Claim 9 is directed at a combination of a compound of claim 1 with certain further active ingredients. Claim 10 is directed at the compound of claim 1 for use as a medicament.

X. The appellant's arguments, in so far as they are relevant to the present decision, can be summarised as follows:

D1 was concerned with the synthesis of steroidal [16α, 17α-*d*]isoxazolidines. The anti-inflammatory activity data provided in it were derived from a topical skin test. Both the objective and the field of application of D1 were different from those of the present application, and starting the assessment of inventive step from compound 19 of D1 was based on hindsight. The comparative experimental tests vis-à-vis compound 18 of D1 in the experimental evidence had to be taken into account. They were indicative of an inventive step.

Reasons for the Decision

Main request

1. Admittance and clarity (Article 84 EPC)

In its communication pursuant to Article 15(1) RPBA, the board raised objections under Article 84 EPC against the claims of main request filed with the

appellant's statement of grounds of appeal. These objections had not been dealt with in the impugned decision.

The board was satisfied that the claims of the appellant's new main request, filed with the letter dated 30 May 2019 in reaction to the board's communication, overcame these objections. Thus, during the oral proceedings, the board decided to admit the new main request into the proceedings.

2. Amendments (Article 123(2) EPC)

Claim 1 is a combination of claims 1, 2 and 9 as filed and now requires, *inter alia*, that both X and Y in formula (I') are fluorine atoms.

Compared to the list of possible alternatives given for R2 in claim 1 as filed, the definition of R2 now comprises only one of these alternatives, namely, "*$(CH_2)_pR8$*". This can be considered a selection from a single list and is allowable.

Furthermore, compared to claim 1 as filed, the disclaimer "*with the proviso that when R2 is (C_1-C_6)alkyl, X and Y are not simultaneously H*" has now been omitted. This amendment is also allowable as the subject-matter to be excluded by the above disclaimer (X = Y = H when R2 = (C_1-C_6)alkyl) cannot fall within the subject-matter of claim 1 anymore by way of limiting both X and Y to fluorine atoms.

Compared to claim 2 as filed, one stereo designation has been changed in claim 1 ("*4a is (R)*" in claim 2 as filed to "*4a is (S)*" in claim 1). This merely amounts to a correction under Rule 139 EPC in view of the

structures given in the application as filed and the notoriously known stereochemistry of corticosteroids.

Claims 2-10 correspond to claims 4-7 and 11-15 as filed.

The board is thus satisfied that the claims of the main request meet the requirements of Article 123(2) EPC.

3. Novelty (Article 54 EPC)

Novelty was not contested in the impugned decision. The board is also satisfied that the claimed subject-matter of the main request is novel over the prior art cited in the impugned decision.

4. Inventive step (Article 56 EPC)

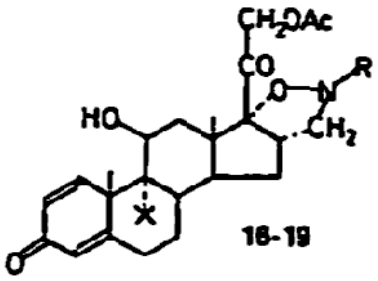
4.1 The present application focuses on conditions of the respiratory tract and on compounds being highly potent and having a long duration of action within the respiratory tract, in particular the lung.

Contrary to the present application, D1 is primarily directed at providing a novel synthetic route to compounds similar to those defined in claim 1 (see point 4.2 below). To show that these compounds are potentially useful as anti-inflammatory agents, they are applied topically to the irritated skin of mice.

In view of the different objectives (present application: provision of a medicament; D1: provision of a synthetic route) and the different fields of application (present application: respiratory tract; D1: skin) it is highly questionable, whether D1 can be considered to represent a suitable starting point for

the assessment of inventive step. For this very reason, inventive step in view of D1 might be acknowledgeable. However, as will be set out hereinafter, even when starting from D1, inventive step can be acknowledged.

4.2 D1 (table I) discloses the following compounds 16-19



with

Compd	X	R
16	H	Me
17	H	CH_2Ph
18	F	Me
19	F	CH_2Ph

to have anti-inflammatory activity in a (modified) croton oil mouse ear assay, i.e. when applied topically to the skin of mice.

The order of potency of compounds 16-19 is as follows (values in brackets are the ratings of D1 with higher numbers representing higher anti-inflammatory activity): 18 (156), 16 (75), 17 (69) and 19 (62).

Thus, among the compounds tested, compound 18 is by far the most active. Compound 19 is the least active.

4.3 As already pointed out in the board's communication pursuant to Article 15(1) RPBA and not contested by the appellant, the compounds of formula (I') in claim 1 are distinguished from compound 19 of D1 only in that they:

i) contain an additional fluorine atom at C-12.

As regards D1, compound 18 differs from compound 19 only in that the former bears a methyl group whereas the latter bears a benzyl group on the nitrogen atom of the isoxazolidine ring. Unlike this benzyl group, this methyl group does not fall within the definition of R2 in formula (I') in claim 1. Thus, compound 18 is structurally more remote from the claimed subject-matter than compound 19. In summary, the compounds of formula (I') in claim 1 are distinguished from compound 18 of D1 in that they:

i) contain an additional fluorine atom at C-12, and
ii) bear a different substituent on the nitrogen atom of the isoxazolidine ring.

Compounds 16 and 17, not containing any fluorine atoms but being otherwise identical to compounds 18 and 19, respectively, are even more remote from the compounds of formula (I') in claim 1 than are compounds 18 and 19.

Thus, compound 19 of D1, i.e. the least active one, comes closest to the compounds of claim 1 in structural terms.

4.4 As set out above (point 4.1), D1 has different objectives and is directed at different fields of application. Therefore, focusing on the structural similarity between the compounds of claim 1 and those of D1 alone would amount to hindsight in the board's view. When starting from D1 as the closest prior art, the skilled person would not have started from the

least active compound tested, i.e. compound 19. They would have started from the most active compound, i.e. compound 18, hoping to retain as much of its activity when moving to a completely different site of application (namely, from the skin to the respiratory tract).

In the board's view, this leaves only compound 18 as a promising starting point for the assessment of inventive step. As set out above, the compounds of formula (I') in claim 1 are distinguished from compound 18 of D1 in that they:

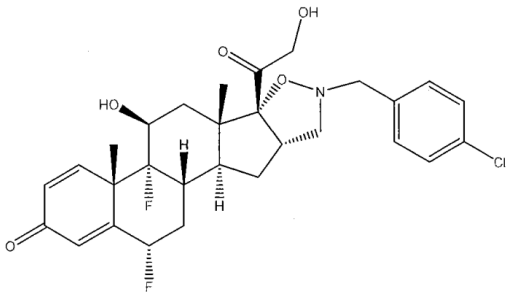
i) contain an additional fluorine atom at C-12, and

ii) bear a different substituent on the nitrogen atom of the isoxazolidine ring.

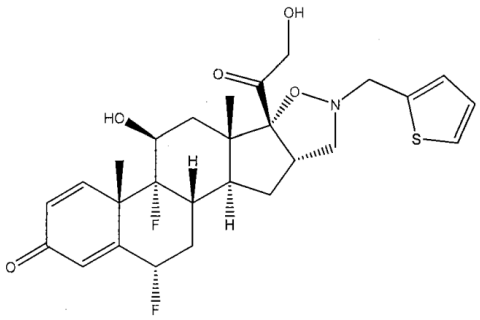
The board in this respect diverges from the decision of the examining division, which saw compound 19 of D1 as the starting point and the additional fluorine atom at C-12 as the **only** distinguishing feature (see in particular point 18) of the decision).

4.5 In the experimental evidence compounds 36 and 37 of the present application, i.e.

compound 36:



compound 37:



are compared with compound 18 of D1. It is found that compounds 36 and 37, i.e. compounds according to claim 1, are potent and show a longer duration of action than compound 18 of D1.

As is clear from the previous paragraphs, the above compounds 36 and 37 are distinguished from compound 18 of D1 in that they i) contain an additional fluorine atom at C-12, and ii) bear a different substituent on the nitrogen atom of the isoxazolidine ring. The experimental evidence obtained for the two compounds does however not allow drawing the conclusion that potential improvements (e.g. a longer duration of action) would necessarily be linked to these distinguishing features. After all, both compounds 36 and 37 of the present application differ from compound 18 of D1 not only with respect to these distinguishing features i) and ii) but also with regard to their substituent on C-6b (compounds 36 and 37 of the present application: $(C=O)CH_2OH$; compound 18 of D1: $C(=O)CH_2OAc$). Nevertheless, in the board's judgement, there is no reason to assume that by replacing the $(C=O)CH_2OH$ substituent of compounds 36 and 37 on the C-6b position by that of compound 18 ($C(=O)CH_2OAc$), anti-inflammatory activity would be lost. Hence, also when making this replacement and thus taking a compound according to claim 1 that in structural terms comes

closest to compound 18 of D1, anti-inflammatory activity can still be assumed to be present.

Thus, when starting from compound 18 of D1, the objective technical problem can be formulated as the provision of alternative anti-inflammatory agents.

4.6 When starting from compound 18 of D1, to arrive at a compound falling within the subject-matter of claim 1, the skilled person would have had to, *inter alia*, replace the methyl group on the nitrogen atom of the isoxazolidine ring with a group falling within the definition of R2 in formula (I') in claim 1. Such a group would e.g. be a benzyl group (R2 being (CH_2)R8 with R8 being phenyl (an aryl)). As can be derived from the structures of the compounds of D1 and their corresponding activities (see above), there is a clear teaching in D1 that compounds bearing a methyl group on the nitrogen atom of the isoxazolidine ring are *per se* more active than the corresponding compounds bearing a benzyl group at this position (see compounds 16 and 18 vs. 17 and 19). Thus, when trying to provide alternative anti-inflammatory agents, the skilled person would have retained this methyl group on the nitrogen atom. This would not have led them to something falling within the subject-matter of claim 1.

Therefore, the subject-matter of claim 1 is considered to involve an inventive step. The same reasoning applies *mutatis mutandis* to dependent claims 2-5 and to the other independent claims 6-10.

The claims of the main request are therefore 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 on the basis of claims 1 to 10 of the main request filed with letter dated 30 May 2019, and a description to be adapted thereto.

The Registrar: The Chairman:

N. Maslin M. O. Müller

Decision electronically authenticated