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Datasheet for the decision of 12 September 2023

Case Number: T 2887/18 - 3.3.02

Application Number: 13152340.9

Publication Number: 2604620

IPC: C07H19/06, C07H19/10, A61K31/7068, A61P31/14

Language of the proceedings: EN

Title of invention:
Modified fluorinated nucleoside analogues

Patent Proprietor:
Gilead Pharmasset LLC

Opponents:
Medici Senza Frontiere Onlus et al
Médecins du Monde et al
AIDES
Gillard, Richard Edward

Headword:

Relevant legal provisions:
EPC Art. 54, 56, 76(1), 83
RPBA 2020 Art. 13(2)

Keyword:
Novelty
Enabling disclosure
Inventive step
Divisional application - added subject-matter
Amendment to appeal case

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2887/18 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 12 September 2023

Appellant 1: (Opponent 1)	Medici Senza Frontiere Onlus et al Via Magenta, 5 00185 Roma (IT)
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Appellant 2: (Opponent 2)	Médecins du Monde et al 62 rue Marcadet 75018 Paris (FR)
Representative:	Jorget, Quentin J-INVENT 110, rue Vieille du Temple 75003 Paris (FR)
Appellant 3: (Opponent 3)	AIDES et al 14 rue Scandicci 93508 Pantin Cedex (FR)
Representative:	Jorget, Quentin J-INVENT 110, rue Vieille du Temple 75003 Paris (FR)
Appellant 4: (Opponent 4)	Gillard, Richard Edward Thavies Inn House 3-4 Holborn Circus London EC1N 2HA (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)

Respondent: (Patent Proprietor)	Gilead Pharmasset LLC c/o Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 (US)
Representative:	Marks & Clerk LLP 15 Fetter Lane London EC4A 1BW (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 October 2018 concerning maintenance of the European Patent No. 2604620 in amended form**

Composition of the Board:

Chairman	M. O. Müller
Members:	S. Bertrand
	M. Blasi

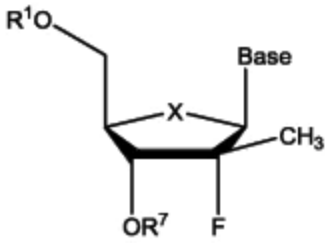
Summary of Facts and Submissions

I. The appeals by opponents 1 to 4 ("appellants 1 to 4") lie from the interlocutory decision of the opposition division that European patent No. 2 604 620 in amended form in accordance with the main request comprising the set of claims filed on 13 July 2018 met the requirements of the EPC.

II. The following documents are referred to in the present decision:

D1	WO 01/92282 A2
D2	WO 2004/002999 A2
D3	WO 01/92282 A2
D6	K.W. Pankiewicz, Carbohydrate Research 327 (2000), pages 87-105
D7	WO 2005/003147 A2
D12	WO 02/57425 A2
D71	Annex 2 concerning lack of enabling disclosure of D2
D78	Idenix statement of grounds of appeal concerning T 1475/16
A090	Preliminary opinion of board of appeal in appeal case T 1475/16 concerning European patent No. 1 523 489

III. Claim 1 in accordance with the main request held allowable by the opposition division relates to a nucleoside (β-D or β-L) or a pharmaceutically acceptable salt thereof of the structure:



IV. In the impugned decision, the opposition division's conclusions included the following:

- The claims in accordance with the main request met the requirements of Article 76(1) EPC.

- The invention as defined in the main request was sufficiently disclosed within the meaning of Article 83 EPC.

- The subject-matter of the claims of the main request was novel in view of the disclosure of D2. The relevant parts of D2 were not an enabling disclosure.

- The subject-matter of the claims of the main request involved an inventive step in view of any of D1, D2, D3 and D12 as the closest prior art.

V. In their statement of grounds of appeal, appellants 1 to 3 contested the reasoning of the opposition division. They submitted that the claims in accordance with the main request added subject-matter and that the invention defined in the claims in accordance with the main request was insufficiently disclosed. Furthermore, the subject-matter of the claims of the main request was not novel in view of D2 and did not involve an inventive step in view of D1, alone or in combination with D6, or in view of D2 alone.

VI. In its statement of grounds of appeal, appellant 4 raised objections of added subject-matter and lack of

novelty in view of D2, and inventive step in view of any of D1 to D3 and D12 alone.

VII. In its reply to the grounds of appeal, the respondent provided counter-arguments regarding added subject-matter, sufficiency of disclosure, novelty and inventive step. In a further letter, the respondent submitted A090 (which it denoted D88).

VIII. In further letters, appellant 4 provided further submissions regarding the allowability of the claims of the main request. Appellant 4 withdrew the request for oral proceedings and announced that it would not be attending oral proceedings.

IX. The board summoned the parties to oral proceedings, as requested by the parties, and issued a communication under Article 15(1) RPBA 2020.

X. Oral proceedings before the board were held by videoconference on 12 September 2023 in the absence of appellant 4, pursuant to Rule 115(2) EPC and Article 15(3) RPBA 2020.

XI. The parties' requests relevant to the decision were as follows:

Appellants 1 to 4 requested that the decision under appeal be set aside and that the patent be revoked.

The respondent requested:

- that the appeal be dismissed, implying that the main request held allowable by the opposition division be upheld and the patent be maintained as amended in the form of the main request, or

- alternatively that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 and 2 filed on 13 July 2018.

XII. The appellants' cases and the respondent's case are summarised in the Reasons below.

Reasons for the Decision

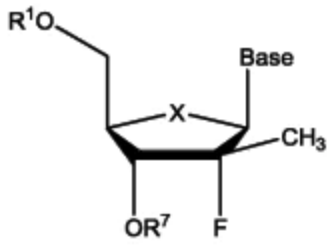
Main request

1. Article 76(1) EPC - Claim 1

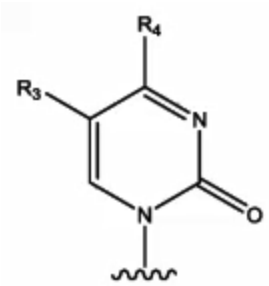
1.1 The patent was granted on a divisional application. This is derived from parent application EP 04 775 900.6. The parent application had been filed as an international application published as WO 2005/003147 (D7).

Claim 1 of the main request reads as follows:

"*1. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β-D or β-L) or a pharmaceutically acceptable salt thereof of the structure:*



wherein the Base is a pyrimidine base represented by the following formula



X is O;

R^7 is H and R^1 is a monophosphate, a diphosphate, or a triphosphate; or

R^1 and R^7 are H;

R^3 is H; and

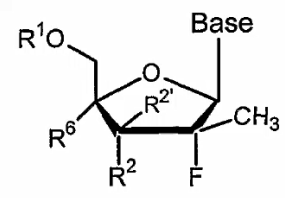
R^4 is NH_2 or OH."

1.2 Appellants 1 to 4 objected that the subject-matter of claim 1 of the main request extended beyond the content of D7.

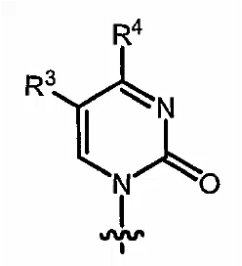
1.3 As submitted by the respondent, claim 1 of the main request is based on the combination of the tenth or twelfth embodiment (pages 38 and 39 of D7) and the passage from page 42, line 6 to the top of page 43 of D7.

The tenth and twelfth embodiments disclosed in D7 read as follows:

"*In a tenth embodiment, a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside or its pharmaceutically acceptable salt or prodrug thereof is provided of the structure*

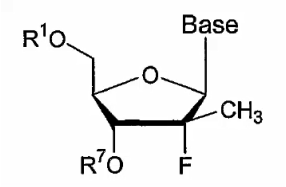


wherein Base is:

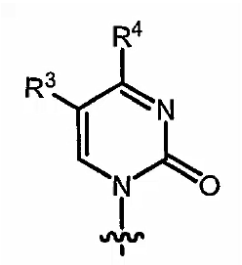


and wherein R^1 is H, R^2 is OH, $R^{2'}$ is H, R^3 is H, R^4 is NH_2 or OH, and R^6 is H."

"In a twelfth embodiment, a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside or its pharmaceutically acceptable salt or prodrug thereof is provided of the structure



wherein Base is:

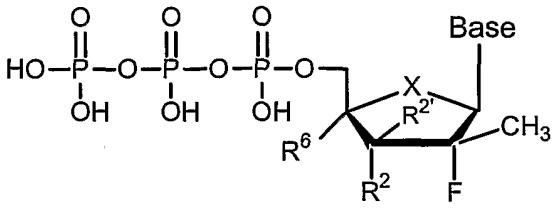


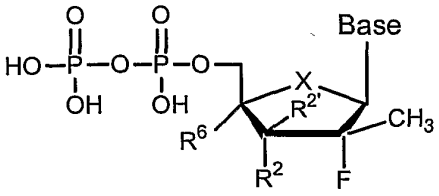
and wherein R^1 is H, R^3 is H, R^4 is NH_2 or OH, and R^7 is H."

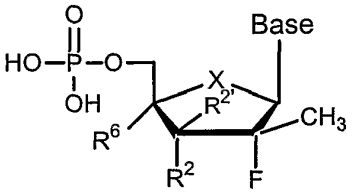
Considering the definition of R^2 (OH), $R^{2'}$ (H) and R^6 (H) given for the tenth embodiment and the definition of R^7 (H) in the twelfth embodiment, the tenth embodiment is identical to the twelfth embodiment.

R^1 in claim 1 of the main request is H, a monophosphate, a diphosphate or a triphosphate. R^1 in the tenth or twelfth embodiment of D7 is restricted to H only. Hence the tenth and twelfth embodiments provide a basis for the alternative in claim 1 with R^1 being H.

The passage from page 42, line 6 to the top of page 43 of D7 discloses that the "*compounds of the present invention*" include 5'-tri-, di- and monophosphate esters. The formulae of these phosphate esters disclosed in the passage are reproduced below:







wherein Base, X, R^2, $R^{2'}$ and R^6 are as defined above.

In the above formulae, the primary carbon atom (the carbon atom at the 5' position) is substituted with a mono-, di- or triphosphate ester. The above formulae correspond to the specific formula of the tenth and twelfth embodiments, with R^1 being mono-, di- or

triphosphate, when Base, X, R^2, $R^{2'}$ and R^6 are as defined in the tenth and twelfth embodiments.

Hence the alternatives of claim 1 with R^1 being mono-, di- or triphosphate find a basis in the combination of the tenth or twelfth embodiment with the above-cited passage on pages 42 and 43 of D7.

1.4 Appellants 1 to 3 argued that in view of the wording "*wherein Base, X, R^2, $R^{2'}$ and R^6 are as defined above*" found on pages 42 and 43 of D7 under the formula of the 5'-mono-, di- and triphosphate esters, a multiple selection of Base, X, R^2, $R^{2'}$ and R^6 substituents was required to arrive at the mono-, di- and triphosphate esters of claim 1 of the main request. These multiple selections added subject-matter.

The board is not convinced. The question to be answered was whether the passage on pages 42 and 43 of D7 disclosing the mono-, di- and triphosphate esters directly and unambiguously refers to the tenth or twelfth embodiments in the preceding text, where the base, X, R^2, $R^{2'}$ and R^6 are defined as in claim 1 of the main request. Since the passage refers to the "compounds of the present invention", it is directly and unambiguously clear to the skilled person that any compound of the invention, including that of the tenth or twelfth embodiment, can be a 5'-mono-, -di- or -triphosphate ester. There is thus no multiple selection of specific substituents required in order to arrive at the alternatives with R^1 being mono-, di- or triphosphate as defined in claim 1 of the main request.

1.5 Appellant 4 submitted that the passage on pages 42 and 43 of D7 referred only to the general formula of the first embodiment disclosed on pages 31 and 32 of D7. It did not refer to the tenth or twelfth embodiment. There

was no link in D7 between the disclosure on pages 42 and 43 and the tenth or twelfth embodiment.

The board disagrees with appellant 4. As set out above, the passage on pages 42 and 43 of D7 refers to the "compounds of the present invention", and thus does not restrict the embodiments. Thus the passage on pages 42 and 43 is a general statement that is understood by the skilled person as referring to any of the embodiments disclosed in D7.

1.6 For the reasons set out above, claim 1 of the main request meets the requirements of Article 76(1) EPC.

1.7 The appellants also objected that claims 2 and 3 of the main request, referring to a mono-, di- or triphosphate (R^1), added subject-matter for the same reasons as those given for claim 1 of the main request.

In view of the above, the board concludes that claims 2 and 3 of the main request meet the requirements of Article 76(1) EPC for the same reasons as for claim 1 of the main request.

2. Sufficiency of disclosure

2.1 Appellants 1, 2 and 3 objected that there was insufficient disclosure of the compounds of claim 1 of the main request. They submitted that no synthetic protocol was given in the application as filed for preparing uridine derivatives (i.e. derivatives with R^4 being OH in the formula of claim 1 of the main request) and phosphate derivatives (i.e. derivatives with R^1 being a monophosphate, a diphosphate or a triphosphate). The application as filed did not disclose the method of preparation, the purification

and the starting material for obtaining the uridine derivatives of claim 1 of the main request.

2.2 The board does not find appellants 1 to 3's submission convincing.

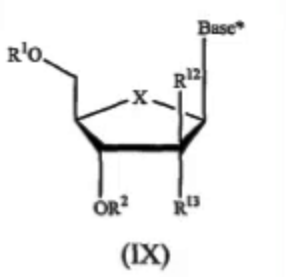
As submitted by the respondent, it is established case law that a successful objection of insufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts. In the present case, no facts evidencing that the uridine derivatives or the phosphate derivatives of claim 1 of the main request cannot be prepared have been submitted by the appellants.

2.3 The board concludes that the invention as defined in claim 1 of the main request is sufficiently disclosed within the meaning of Article 83 EPC.

3. Novelty

3.1 Appellants 1, 2, 3 and 4 submitted that the subject-matter of claim 1 of the main request lacked novelty in view of the disclosure of D2, more specifically in view of formula (IX) on page 100 in combination with the passages on page 100, lines 27 to 29 and page 104, lines 15 to 27.

3.2 Formula (IX) on page 100 of D2 is reproduced below:



(IX)

In the passage on page 100, lines 24 to 29, Base* is defined as a purine or pyrimidine base, R^{12} is $C(Y^3)_3$, R^{13} is fluoro, X is O, Y^3 is H, and R^1 to R^3 are also H.

X, R^1 and R^2 in formula (IX) as defined above correspond to the definition of the X, R^1 and R^7 groups in the formula of claim 1 of the main request. R^{12} in combination with Y^3 (CH_3) in the above formula of D2 represents the methyl group in the formula of claim 1 of the main request. R^{13} (fluoro) in the above formula corresponds to the fluorine atom in the formula of claim 1 of the main request.

In the passage on page 104, lines 15 to 27 of D2, it is disclosed that Base* (defined on page 100 as a purine or pyrimidine base) may be cytosine (page 104, line 19) or uracil (line 20 of the same page), corresponding to the base required by claim 1 of the main request (when, in the formula of claim 1 of the main request, R^4 = NH_2 the base is cytosine, and when R^4 = OH the base is uracil).

Thus only one selection of the base "Base*" is needed in D2 to arrive at the subject-matter of claim 1 of the main request. The need for a single selection does not establish novelty. This was common ground between the parties.

The respondent argued that the compounds of formula (IX) of D2 were nevertheless not novelty-destroying, since these compounds were not disclosed in an enabling manner in D2.

3.3 In fact, in the appealed decision, the opposition division concluded that the above specific disclosure of D2 did "*not provide for an enabling disclosure to the relevant 2'-fluoro nucleosides...*" (point 6 of the decision, second full paragraph on page 18). The

opposition division's reasoning included that the type of nucleosides having a 2'-fluoro (down) and 2'-methyl (up) substitution, as referred to in D2, was unprecedented. Such nucleosides were to be prepared from the corresponding 2'-hydroxy nucleoside. The corresponding 2'-hydroxy nucleoside was fluorinated with a fluorinating agent DAST. However, it was rather difficult to introduce a fluorine atom at the C-2 position of the 2'-hydroxy nucleoside, as known from D6.

3.4 The board agrees with the respondent and the decision under appeal for the following reasons.

It was undisputed that D2 comprises no example disclosing the preparation of a compound of formula (IX).

D2 discloses in section B starting on page 122 a general synthesis of "*2'-C-Branched Nucleosides*", under which compounds of formula (IX) fall. This section comprises schemes 3 and 4. However, contrary to appellants 1 to 3's submissions, there is in these schemes no teaching as to how a compound having a 2'-fluoro (down) and 2'-methyl (up) substitution at the 2' position of the ribose ring as present in formula (IX) of D2 can be prepared, and no teaching of the suitable starting material for preparing such a compound, let alone any teaching of a method for synthesising a fluorinated compound of formula (IX) starting from the deprotected nucleoside having a 2'-hydroxy (down) and 2'-R^6 (up) substitution, the starting material needed to prepare this compound according to appellants 1 to 3.

Even if one were to start from the deprotected nucleoside having a 2'-hydroxy (down) and 2'-R^6 (up)

substitution disclosed in schemes 3 and 4 of D2, the skilled person would not have arrived at the corresponding compound of formula (IX) in view of the conclusion drawn in D71.

D71 is a document filed by the respondent in the proceedings before the opposition division. It comprises submissions made during the opposition proceedings of the patent granted on the basis of D2 and regarding lack of enabling disclosure of compounds of formula (IX). D71 was submitted to show that the skilled person would not have been able to prepare a compound of formula (IX), having a 2'-fluoro (down) and 2'-methyl (up) substitution at the 2' position of the ribose ring based on the information provided in D2 and the common general knowledge at the filing date of D2 (27 June 2003).

First, D71 summarises the experiments conducted by a skilled team of chemists and collaborators belonging to the applicants of D2 (Idenix) between 2002 and 2005. This skilled team failed to make a compound of formula (IX) until D7 was published on 13 January 2005 (point 4.35 of D71). This was not contested by the appellants.

Second, the skilled team tried different synthetic routes starting from different starting materials (point 4.36 of D71) and using different fluorinated reagents (point 4.37 of D71) without affording a compound of formula (IX) within the period 2002 to 2005. These submissions were not disputed by the appellants either.

Thus D71 provides evidence that, starting from the deprotected nucleoside having a 2'-hydroxy (down) and 2'-R^6 (up) substitution disclosed in schemes 3 and 4 of

D2, the skilled person would not have arrived at the corresponding compound of formula (IX).

3.5 Appellants 1 to 3 relied on D78 and submitted that the skilled team of chemists and collaborators overlooked the fact that the claimed product was obtained in one of the initial syntheses. They submitted that, based on the same prior-art information, namely the conversion of 2'-hydroxy nucleosides into 2'-fluoro nucleosides using a fluorinating agent, compounds of the invention could have been prepared as evidenced by D78.

The board disagrees.

In that initial synthesis, the skilled team attempted to fluorinate a protected 2'-methyl (down) 2'-hydroxy (up) compound with deoxo-Fluor, an analogue of DAST which fluorinates via the same mechanism as DAST, namely inversion of the configuration of the carbon atom. This attempt was however deemed a failure, and was abandoned in favour of further, different, strategies (point 2.15 of A090).

With regard to this attempt, the appellants essentially argued that the reaction carried out by the skilled team was repeated by Clark and others using DAST instead of deoxo-Fluor (point 122 of D78). However, even accepting the appellants' argument that the skilled team had unknowingly prepared the desired compound of formula (IX), this does not alter the board's position as set out above. Specifically, the fact remains that the evidence on file (D71) does not show that the conversion of 2'-OH nucleosides into 2'-F nucleosides using DAST could succeed. If anything, D71 shows that, for a team of experts, the preparation of the desired compound of formula (IX) amounted to a real-life research project.

For these reasons, appellants 1 to 3's submission is not convincing.

3.6 Appellants 1 to 3 submitted that by acknowledging sufficiency of disclosure while at the same time drawing the conclusion that the compounds of formula (IX) in D2 were not disclosed in an enabling manner, the opposition division did not consistently apply the sufficiency-of-disclosure requirement, which should apply in the same manner to the disclosure of the patent and of the prior art.

The board does not agree. Appellant 1 to 3's submissions in the context of sufficiency of disclosure are not based on the same facts as the submissions on enablement of disclosure of D2. The objection of insufficiency of disclosure is based on the preparation of uridine derivatives and phosphate derivatives, while the disclosure of D2 is based on the introduction of a fluorine atom at the C-2 position of 2'-hydroxy nucleosides.

3.7 In conclusion, the compounds of formula (IX) in D2 are not disclosed in an enabling manner. These compounds are thus not novelty-destroying. The subject-matter of claim 1 of the main request is therefore novel within the meaning of Article 54 EPC.

3.8 During the oral proceedings before the board, appellants 1 to 3 referred to, *inter alia*, D78 and submissions made in writing by appellant 4 for the assessment of enablement of disclosure of D2. The respondent objected to the admittance of appellants 1 to 3's submissions made during the oral proceedings based on D78 and the submissions made in writing by appellant 4 into the proceedings. The board decided to

admit these submissions into the proceedings and considered them in the above reasoning. The resulting decision on novelty in view of D2 is, as set out above, in the respondent's favour, and therefore there is no need to provide reasons for the admittance of these submissions.

4. Inventive step

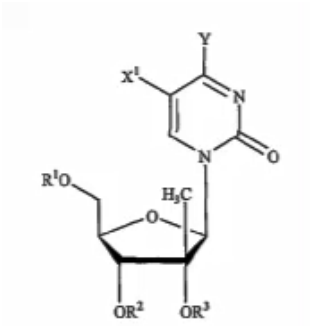
4.1 The aim of the patent is to provide an inhibitor for the treatment of *Flaviviridae* infections, especially inhibitors for the treatment of hepatitis C virus (HCV) infections. The compounds of claim 1 of the main request, as set out above, are characterised by a particular substitution at the 2' position on the ribose ring, namely a fluorine atom (down) and a methyl group (up).

4.2 Appellants 1, 2 and 3 disputed inventive step of the subject-matter of claim 1 of the main request in view of D1 and D2 as the closest prior art. Appellant 4 submitted that the subject-matter of claim 1 of the main request lacked inventive step in view of D1, D2, D3 or D12 as the closest prior art.

4.3 D1 as the closest prior art

D1 discloses nucleoside compounds for the treatment of hepatitis C infections (page 7, lines 15 to 17) and therefore has the same purpose as the patent. D1 can thus be considered to represent suitable closest prior art.

D1 (page 128) relates to compounds of formula (V). The appellants referred in particular to the following compounds:



(V)

with the following substituents:

R^1	R^2	R^3	X^1	Y
H	H	H	H	OH
H	H	H	H	NH_2
monophosphate	H	H	H	OH
monophosphate	H	H	H	NH_2
Diphosphate	H	H	H	NH_2
Diphosphate	H	H	H	OH
Triphosphate	H	H	H	NH_2
Triphosphate	H	H	H	OH

For all the above compounds, R^1, R^2, X^1 and Y correspond to R^1, R^7, R^3 and R^4, respectively, of the compounds according to claim 1 of the main request.

4.3.1 Distinguishing feature

The difference between the compounds of D1 and the compounds of claim 1 of the main request lies in the presence of a fluorine atom in the 2' position of the nucleoside for the claimed compounds instead of a hydroxyl group in the compounds of formula (V) of D1 identified above (R^3 is H).

4.3.2 Objective technical problem

Assuming in the appellants' favour that the claimed compounds do not exhibit any technical effect linked to

the distinguishing feature, the objective technical problem is to provide alternative compounds.

4.3.3 Obviousness

For the reasons given above in the context of the assessment of novelty, a research programme would be (and in fact was) needed to arrive at the compounds having the particular fluorine atom (down) and a methyl group (up) substitution at the 2' position on the ribose ring as defined in claim 1 of the main request. Preparation of the claimed compounds was therefore not something which was within the routine of the skilled person. Thus the skilled person, starting from D1 and faced with the above-mentioned problem, would not have arrived at the claimed compounds. For this reason alone, the claimed compounds are not obvious in view of D1.

4.3.4 Appellants 1 to 3 relied on document D6 (pages 87 and 88) and submitted that, to solve the problem of providing a mere compound, all structures were obvious. D6 disclosed nucleosides fluorinated at the 2' position on the ribose ring, and thus gave motivation to the skilled person to prepare the compounds of claim 1 of the main request.

Appellants 1 to 3's argument is not convincing.

D6 is a scientific article relating to fluorinated nucleosides. The sentence bridging pages 87 and 88 referred to by appellants 1 to 3 reads "*Since some early-synthesized 2'-deoxy-2'-fluoro nucleosides showed promising therapeutic potential (mainly antiviral and anticancer), the synthesis of new generations of 2'-fluorinated nucleosides flourished in hope of new drug discovery.*" However, as submitted by the respondent, D6 discloses nucleosides having only one

single substituent or two fluorine atoms at the 2' position. D6 does not disclose nucleosides having the particular fluorine atom (down) and methyl group (up) substitution at the 2' position required by claim 1 of the main request. Furthermore, as submitted by the respondent, D6 does not teach the skilled person how to make a nucleoside having a fluorine atom (down) and a methyl group (up) substitution at the 2' position on the ribose ring.

Thus the teaching of D6 does not change the conclusion drawn above that the skilled person would not have arrived at the compounds having the particular fluorine atom (down) and a methyl group (up) substitution at the 2' position on the ribose ring as defined in claim 1 of the main request.

4.3.5 Inventive step starting from D1 can thus be acknowledged.

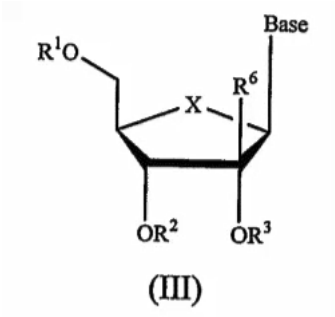
4.4 D2 as the closest prior art

D2 relates to nucleoside prodrugs for the treatment of *Flaviviridae* infections, such as HCV infections (page 1, lines 10 to 13 of D2), and therefore has the same purpose as the patent. Hence D2 can also be considered to represent the closest prior art.

Appellants 1 to 3 first submitted that, starting from the disclosure on page 100 of D2 and the compounds of formula (IX), the objective technical problem was the provision of a method to synthesise the compounds of claim 1 of the main request. The obstacles alleged in the context of the enablement determination could be easily overcome by the skilled person, as was evidenced by e.g. D78.

The board disagrees. As set out above in the context of novelty, the disclosure on page 100 of D2 is not enabling. This implies that inventive skill is needed to prepare the compounds of formula (IX) of D2. Therefore the disclosure of compounds of formula (IX) in D2 cannot be prejudicial to inventive step of the subject-matter of claim 1 of the main request.

4.5 Appellants 1 to 3 also referred to the compounds of formula (III) on page 19 of D2:



(III)

and the definition of the groups of formula (III) on pages 20 to 26. In formula (III) of D2, Base may be formula (F) on page 20, which covers uracil (when Y in formula (F) is OH) or cytosine (when Y in formula (F) is NH_2), as required by claim 1 of the main request when R^4 is OH or NH_2. R^1 and R^2 in formula (III) of D2 may be phosphate (including mono-, di- or triphosphate and a stabilised phosphate), and R^3 may be a hydrogen atom (page 17, lines 24 and 25; page 25, line 9). R^6 may be CH_3 (page 26, line 28).

As submitted by appellants 1 to 3, the distinguishing feature of claim 1 of the main request in view of formula (III) of D2 is the presence of a fluorine atom in the 2' position of the nucleoside for the claimed compounds instead of a hydroxyl group in the compounds of formula (III) of D2 identified above (R^3 is H).

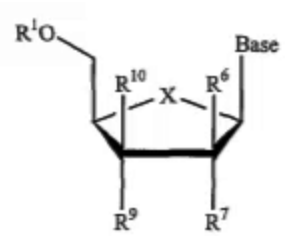
The distinguishing feature of claim 1 of the main request in view of formula (III) of D2 is thus the same as that identified in view of D1 as the closest prior art.

Therefore the reasoning given in view of D1 as the closest prior art applies to the objection based on formula (III) of D2 as the closest prior art. Inventive step in view of D2 as the closest prior art can thus be acknowledged.

4.6 D3 as the closest prior art

D3 relates to antiviral nucleoside prodrugs for the treatment of flavivirus infections (page 4, lines 6 to 9 of D3). Like D1 and D2, this is the same purpose as the patent. Hence D3 can also be considered to represent the closest prior art.

D3 discloses nucleosides of formula (XVII) on page 37:



(XVII)

Page 41 of D3 discloses a "subembodiment" wherein Base is cytosine; R^1 is hydrogen; R^6 is methyl; R^7 and R^9 are hydroxyl; R^{10} is hydrogen; and X is O.

It follows that the distinguishing feature of claim 1 of the main request in view of formula (XVII) of D3 is the presence of a fluorine atom in the 2' position of the nucleoside for the claimed compounds instead of a hydroxyl group in the compounds of formula (XVII) of D3 identified above (R^7 is OH). This distinguishing

feature is the same as that identified in view of D1 as the closest prior art.

Thus the reasoning given in view of D1 as the closest prior art applies to the objection based on formula (XVII) of D3 as the closest prior art. Inventive step in view of D3 can thus be acknowledged.

4.7 D12 as the closest prior art

Appellant 4 submitted that D12 disclosed nucleosides, and the distinguishing feature of claim 1 of the main request in view of D12 was the same as that identified in view of D1. This was not disputed by the respondent.

Thus the reasoning given in view of D1 as the closest prior art applies to the objection based on D12 as the closest prior art.

4.8 It follows that the subject-matter of claim 1 and by the same token of claims 2 to 7 of the main request involves an inventive step within the meaning of Article 56 EPC in view of any of D1, D2, D3 and D12 as the closest prior art.

5. Admittance of the objection of lack of inventive step with D12 as secondary document

5.1 During the oral proceedings, appellants 1 to 3 raised an objection of lack of inventive step starting from D2 as the closest prior art in combination with D12. They submitted *inter alia* that the claimed subject-matter would have been obvious, as the skilled person, faced with the above-mentioned problem of providing alternative compounds, would have used a nucleoside having at the 2' position on the ribose ring a hydroxyl group (up) and a methyl group (down), this substitution

at that position being known from D12, in particular example 61.

5.2 The respondent objected to the admittance of this objection.

5.3 These submissions consisted of new allegations and represented an amendment to appellants 1 to 3's cases. Since they were made for the first time during oral proceedings before the board, their admittance is governed by Article 13(2) RPBA 2020.

In accordance with Article 13(2) RPBA 2020, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

Since the main request was filed before the opposition division, the objection of lack of inventive step of the subject-matter of claim 1 with D12 as secondary document could have been made at an earlier stage. The board sees no reason, and no reason has been submitted by appellants 1 to 3, why this was not done. There are thus no exceptional circumstances which might justify the allegations made by appellants 1 to 3 only during the oral proceedings.

5.4 For these reasons, the board decided not to admit the objection of lack of inventive step with D12 as secondary document into the proceedings, in accordance with Article 13(2) RPBA 2020.

6. The main request is allowable.

Order

For these reasons it is decided that:

Appellants 1 to 4's appeals are dismissed.

The Registrar: The Chairman:

M. Schalow M. O. Müller

Decision electronically authenticated