Lionel Vial
Conseil en Propriété Industrielle - European Patent Attorney

Via Epoline

European Patent Office
80298 Munich
Germany

Gif-sur-Yvette, 10 February 2015

Opposition against patent EP 2 203 462, filed on 26 March 2008
In the name of Gilead Pharmasset LLC
For « Nucleoside Phosphoramidate Prodrugs »

N. Réf. : C000016

Dear Sirs,

We hereby give notice of opposition against patent EP 2 203 462 pursuant to Article 99 EPC.

The opponent is Médecins du Monde.

The notice of opposition is filed electronically, along with a statement of facts, evidence and arguments, and copies of cited documents.

Yours faithfully,

Lionel Vial
Professional representative before the EPO

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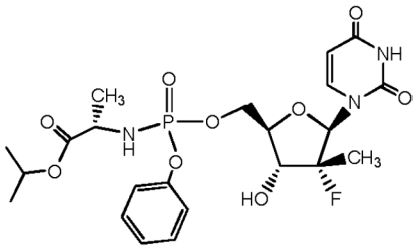
Opposition to patent EP 2 203 462 (Gilead Pharmasset LLC)

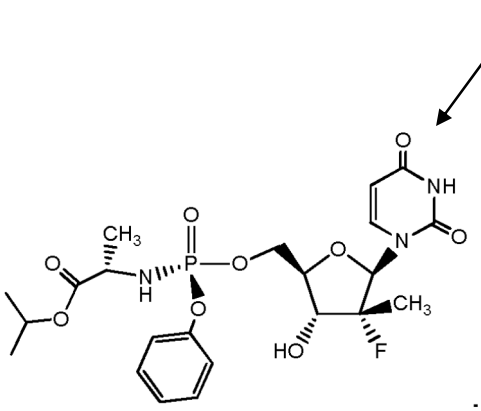
Facts, evidence and arguments in support of the grounds of opposition

Introduction

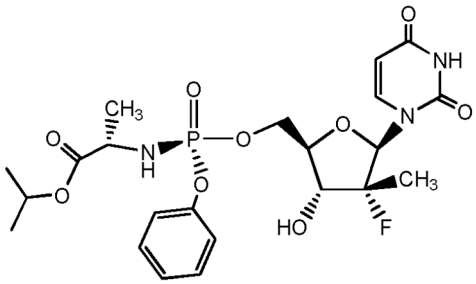
Patent EP 2 203 462, hereafter the opposed patent, claims 3 compounds (claims 1-3) as well as compositions comprising these compounds and a pharmaceutically acceptable medium (claims 4-6):



Claim 1 (PSI-7851)



Claim 2 (PSI-7977 – Sofosbuvir)

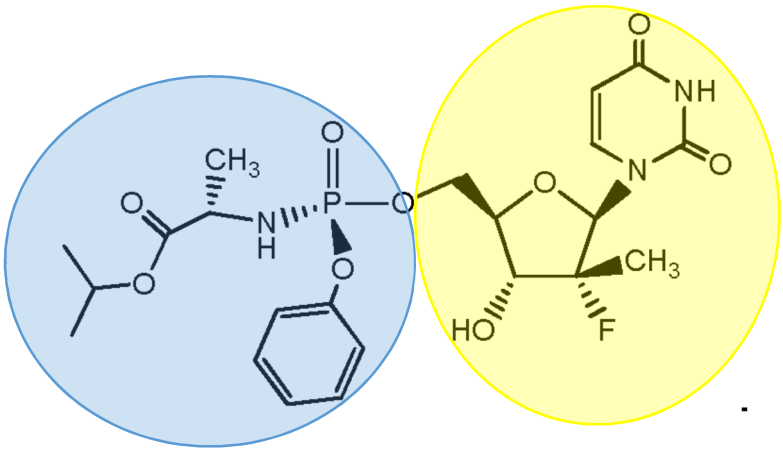


Claim 3 (PSI-7976)

The compound of claim 1, also referred to as PSI-7851 in the art, is comprised of two stereoisomers at the P-center of stereochemistry, which are respectively claimed in claim 2 and claim 3.

The compound of claim 2, also referred to as PSI-7977, is Sofosbuvir (INN). Sofosbuvir is the active principle of Sovaldi®, a drug indicated for the treatment of HCV infections.

The claimed compounds are comprised of two parts, a nucleoside analog moiety and a phosphoramidate moiety:



Phosphoramidate Nucleoside analog

The nucleoside analog is derived from β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine, also known as RO2433 in the art, and the phosphoramidate is the phenyl-phosphoramidate of L-alanine isopropyl ester.

Sofosbuvir crosses biological membranes to reach the intracellular medium, where it yields β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine-monophophosphate (RO2433-MP) upon hydrolysis of the phenyl and L-alanyl groups. RO2433-MP is then phosphorylated to RO433-DP and RO2433-TP, which inhibits HCV RNA-dependant RNA polymerase (RdRp), also known as NS5B.

In contrast, β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine (RO2433) is inactive against HCV, seemingly because it is a poor substrate for the kinase performing the first phosphate addition. Sofosbuvir allows overcoming this blockade by acting as a pro-nucleotide, *i.e*. a compound which yields an already phosphorylated nucleoside.

By way of example, for 12 weeks of treatment, Sovaldi® is currently priced at 41 000 € in France and 44 000 € in the United-Kingdom. In view of this pricing, several countries have not recommended Sovaldi® for prescription to all HCV-infected individuals, to safeguard their public health systems, even though this first NS5B-inhibitor to be marketed offers significant advantages over existing treatments. Thus, in Europe alone, several hundred thousand individuals who could benefit from a treatment with Sofosbuvir find themselves excluded from this treatment for economic reasons.

This situation is notably the result of the monopoly granted over Sofusbuvir by the opposed patent, which prevents other actors to offer Sofosbuvir at lower prices.

However, this monopoly has been unduly awarded as the alleged contribution to the art of the proprietor of the patent does not justify such a reward. Thus, corresponding patents and patent applications in other countries have already been challenged, in particular by the Initiative for Medicines, Access & Knowledge (I-MAK).

Indeed, in stark contrast to the principles set forth in decision T 1063/06 of 3 February 2009, the opposed patent, which, at its effective date, is merely a list of thousands of compounds, of unknown activity for the most part, clearly aimed at reserving an unexplored field of research instead of protecting factual results of successful research as a reward for making concrete technical results available to the public. Thus, Sofosbuvir itself does not have any support in

the application as filed. This leads to the following objections under Articles 100(b) and (c) EPC.

Moreover, Sofosbuvir in fact follows from the normal evolution of technic, simply aggregating the contributions of various researchers from the scientific community. Thus, the nucleoside analog found in Sofosbuvir was known in the art (see D10 and claim 40 of D12) and the use of phosphoramidates, such as the phenyl-phosphoramidate of L-alanine isopropyl ester found in Sofosbuvir, was also well documented in the art as a means to provide antiviral nucleotide analogs by bypassing the blockade of the first phosphorylation (see D4, D5, D7 and D11). This gives rise to the following objections under Article 100(a) EPC.

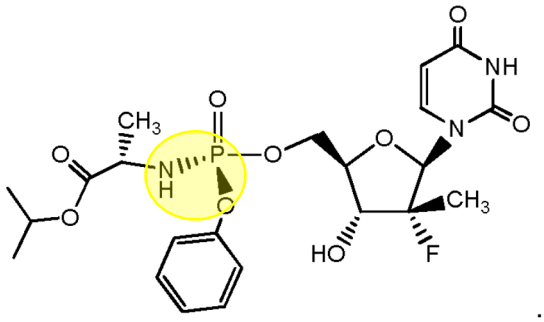
Cited documents

Number	Description of the document	Date of availability to the public
D1	Assignment of US provisional application n°60/909,315	Not applicable
D2	Assignment of US provisional application n°60/982,309	Not applicable
D3	Assignment of US patent application n°12/053,015	Not applicable
D4	WO 2005/012327 A2	10 February 2005
D5	Thesis entitled “Design, Synthesis and Biological Evaluation of Novel Nucleotide Prodrugs as Potential Anti-Hepatitis C Virus Agents” submitted by Plinio Perrone	February 2007
D6	Ma *et al*. (2007) *J. Biol. Chem*. **282**:29812-29820	12 October 2007
D7	Perrone *et al*. (2007) *J. Med. Chem.* **50**:1840-1849	17 March 2007
D8	Poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses which was held in Glasgow (Scotland) on 9-13 September 2007	September 2007
D9	Murakami *et al*. (2008) *Antimicrob. Agents Chemother*. **52**:458-464	12 November 2007
D10	Clark *et al*. (2005) *J. Med. Chem*. **48**:5504-5508	26 July 2005
D11	Zemlicka (2002) *Biochimica et Biophysica Acta* **1587**:276-286	18 July 2002
D12	WO 2005/003147 A2	13 January 2005

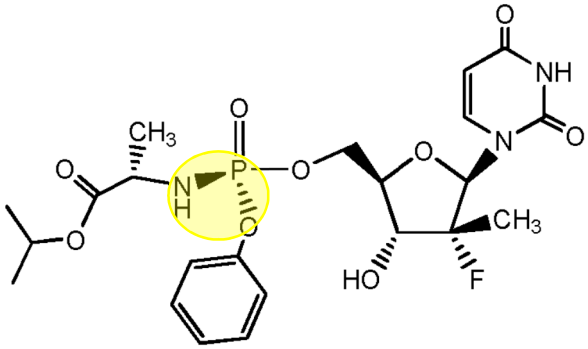
N.B. The priority documents, the opposed patent, as well as international application WO 2008/121634 from which the opposed patent originates, are also cited in the present statement but are not provided, as they are part of the Examination dossier and can be readily accessed.

1. The subject-matter of the European patent extends beyond the content of the application as filed (Article 100(c) EPC)

Opposed claim 2 relates to a compound represented by the formula:



Opposed claim 3 relates to a compound represented by the formula:



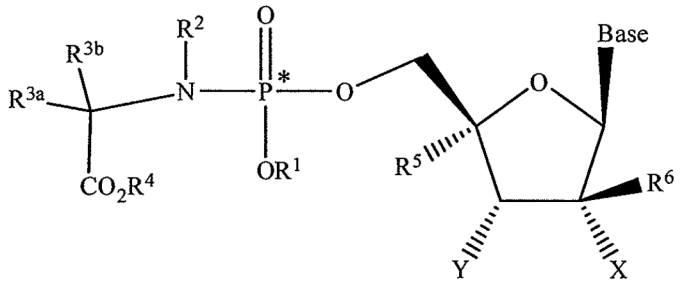
These two structures represent the two possible stereochemical configurations at the phosphorus (circled above) of the compound of claim 1.

During Examination, the patentee explained that the support for the subject-matter of opposed claims 2 and 3 could be found on page 20, lines 8-16 and in Example 81, on pages 692-693 of the application as filed[1] (letter of the applicant's representative of 25 October 2010) as well as from compound IX-25-2 when read with description page 99-100 of the application as filed (letter of the applicant's representative of 14 January 2014).

However, the above structures are not depicted as such in any part of the application as filed. In fact no individual compound having a specific stereochemical configuration at the phosphorus atom is disclosed in the application as filed.

Thus, the paragraph from line 8 to 16 on page 20 is no more than a general statement according to which the applicants contemplate the use of the racemate and/or the resolved enantiomers, seemingly in relation with the chirality at phosphorus of formula I.

[1] When reference is made to the content of the application as filed in the following, the page and line numbers are those of the published international application from which the opposed patent derives



Formula I

Example 81 on pages 692-693 relates to the separation of a “fast moving isomer” and a “slow moving isomer”, in relation to their respective elution times, from a chromatography column fed with the mixtures of diastereoisomers at the P-chiral center of the compounds of Examples 15, 39 and 49. However, the absolute stereochemistry of the P-chiral centers of the diastereoisomers were not determined.

As for the paragraph on pages 99-100, it recites that:

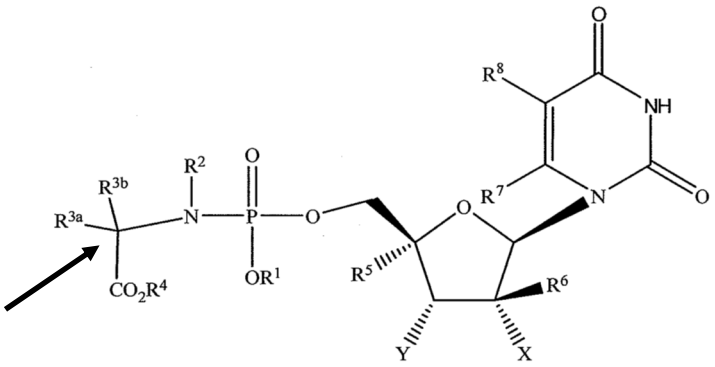
“*Although the structures below do not specifically depict chirality at phosphorus, the inventors recognize that stereochemical configurations are possible such that in a staggered (or zig-zag) line structure the oxo-substitutent projects away from the viewer, and vice versa, i.e., where the Cahn-Ingold-Prelog stereochemical designation of phosphorous is either R or S. Therefore, the structures below include all possible stereochemical configurations possible for phosphorus*.” (underlining added)

It was considered, in the course of Examination, that this paragraph, as applied to compound IX-25-2, amounted to specifically disclosing the compounds of claims 2 and 3.

However, this is not correct.

In particular, it should be noted that the paragraph of pages 99-100 is intended to be applied to each of the structures II to XXXII and not directly to each one of the 400 sets of 9 substituents which are listed for each structure (for each structure there are 50 tables comprising 8 sets of 9 substituents).

It should also be noted that in addition to the configuration of the phosphorus, the stereochemical configuration of the asymmetric carbon to which are linked R^{3a} and R^{3b} is also not specified in compound IX-25-2:

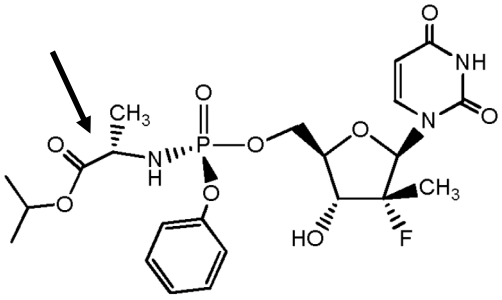


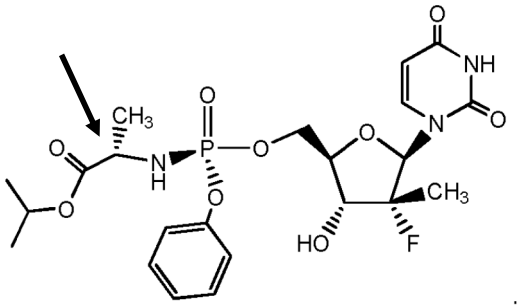
IX

Table IX-25.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-25-2	Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H

In contrast, this carbon is in the S configuration in the compounds of claims 2 and 3:





Thus, the structures depicted in claims 2 and 3 in fact follow on from the selection within **4** lists of substituents or configurations:

1) Selecting one structure from the list consisting of structures II to XXXII
2) Selecting one configuration for the asymmetric carbon from the list consisting of R and S;
3) Selecting one configuration for the phosphorus from the list consisting of R and S;
4) Selecting one set of substituents from the list consisting of set 1 (1-1) to set 400 (50-8).

According to the Guidelines for Examination in the EPO (November 2014 edition, Part G, Chapter VI, Paragraph 8(i)(a)), an individual chemical compound is considered as novel when it results from the selection of specific substituents from two or more "lists" of substituents given in a known generic formula.

In other words, an individual chemical compound cannot be considered as deriving directly and unambiguously from a generic formula when it results from the selection of specific substituents from two or more "lists" of substituents given in the generic formula.

Applied to the present case, this means that the compounds of claims 2 and 3 do not directly and unambiguously derive from the paragraph on pages 99-100 as applied to the following structures, *i.e*. they extend beyond the content of the application as filed.

This also applies to the subject-matter of claims 5 and 6 which depend from claims 2 and 3 respectively.

2. The European patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Article 100(b) EPC)

2.1. The opposed patent does not disclose any stereospecific method of synthesis and/or of purification of compounds of claims 2 and 3.

In particular, it should be noted that Example 81 on pages 692-693 which relates to the separation of a "fast moving isomer" and a "slow moving isomer" from mixtures of diastereoisomers at the P-chiral center is not applied to the compound of claim 1 (*i.e*. Example 25) and nothing indicates that it could be applied to this compound. Besides, the absolute stereochemistry of the P-chiral centers of the diastereoisomers cannot be determined using this method.

Accordingly, the one of skill in the art wishing to obtain the compounds of claims 2 and 3 on the basis of the opposed patent is left with the undue burden of having to devise stereospecific methods of synthesis and/or of purification of these compounds by himself.

Thus, the subject-matter of claims 2 and 3 is not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

2.2. Claims 5 and 6 respectively relate to compositions comprising the compounds of claims 2-3 and a pharmaceutically acceptable medium.

As such, the subject-matter of these claims is also not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art

In addition, inasmuch as claims 5 and 6 aim at protecting pharmaceutical compositions comprising the compounds of claims 2 and 3, that is the first medical use of these compounds, then their subject-matter is also insufficiently disclosed in this regard.

Indeed, as is recalled in the *Case Law of the Boards of Appeal of the EPO*, Seventh Edition (September 2013), Part II, Chapter C, Paragraph 6.2., under Art. 83 EPC [which provisions are similar to that Art. 100(b) EPC], unless this is already known to the skilled person at the priority date, the application must disclose the suitability of the product to be manufactured for the claimed therapeutic application.

In the present case, no data are presented in the opposed patent which show an anti-HCV activity of the compounds of claims 2 and 3.

In addition, it cannot be directly and unambiguously derived from the activity of the compound of Example 25 (*i.e*. the compound of claim 1) presented in Example 82 that its stereoisomers at phosphorus would automatically be active, as, starting from a biologically active racemic mixture, it is often the case that only one of the two enantiomers composing the racemate is active. Thus, by way of example, it is well known that (S)-ibuprofen is over 100-fold more potent an inhibitor of cyclo-oxygenase I than (R)-ibuprofen and accounts for essentially all the COX-I-inhibitory activity presented by racemic ibuprofen.

3. The subject-matter of the European patent is not patentable under Articles 52, 54 and 56 EPC (Article 100(a) EPC

3.1. The priority right is not validly claimed

The opposed patent was filed on 26 March 2008 and claims the benefit of three priority dates:

- 30 March 2007 from US provisional application n°60/909,315 (first priority)
- 24 October 2007 from US provisional application n°60/982,309 (second priority) and
- 21 March 2008 from US patent application n°12/053,015 (third priority).

However, the priority claims are invalid for several reasons.

3.1.1. The Priority right was not assigned to the applicant when the patent was filed

3.1.1.1. The opposed patent was filed in the name of Pharmasset Inc. as the applicant, while the three priority applications were filed in the name of the inventors as applicants.

Article 87 EPC provides that any person who has duly filed, in or for any State party to the Paris Convention for the Protection of Industrial Property or any Member of the World Trade Organization, an application for a patent, a utility model or a utility certificate, or his successor in title, shall enjoy, for the purpose of filing a European patent application in respect of the same invention, a right of priority during a period of twelve months from the date of filing of the first application.

In this regard, it should be recalled that the right of priority is not attached to the application from which it arose and that it may be transferred to a successor in title independently of the transfer or non-transfer of the first application on which it is based, and which can therefore remain with the original applicant or be transferred to a third person (see the *Guide to the Application of the Paris Convention for the Protection of Industrial Property* by G.H.C. Bodhenhausen (1969) page37, paragraph (h), which discusses Article 4, Section A(1) of the Paris Convention on which Article 87 EPC is based).

However, in the present case Pharmasset Inc. cannot be considered the successor in title of the inventors, as the right of priority has not been assigned by the inventors to Pharmasset Inc.

This is apparent from the assignments of US provisional application n°60/909,315 **(D1)**, US provisional application n°60/982,309 **(D2)** and US patent application n°12/053,015 **(D3)** to Pharmasset Inc. by the inventors.

These assignments provide that the inventors "*sell, assign and transfer unto said ASSIGNEE, the full and exclusive right to the said invention in the United States and its territorial possessions and in all foreign countries and the entire right, title and interest in and to any and all Letters Patent which may be granted therefor in the United States and its territorial possessions and in any and all foreign countries and in and to any and all divisions, reissues, continuations, substitutions and renewals thereof*."

There is made no mention of any assignment of the right of priority nor of the right of filing foreign applications, and it is only the ownership of the invention and of the patents which may be granted for this invention which is assigned.

In fact, it can be seen from the following paragraph of the assignment that there is no intent to transfer the right to file foreign applications by claiming the priority of the initial filings under this assignment, as this paragraph provides that the inventors "*authorize and request the Patent Office Officials in the United States and its territorial possessions and any and all foreign countries to issue any and all of said Letter Patent, when granted, to said ASSIGNEE*", *i.e*. the transfer is to take place after the filing with the Patent Offices has been made, necessarily by the inventors.

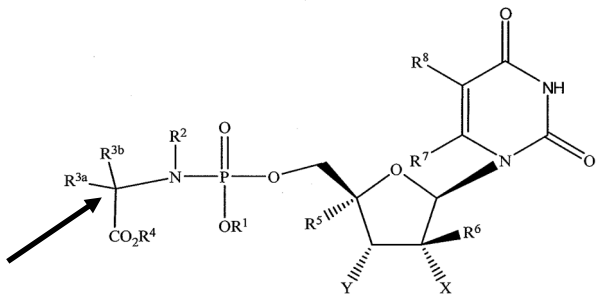
Accordingly, the opposed patent does not benefit from any of the priorities it is claiming and its effective date is 26 March 2008.

3.1.1.2. In addition, even if it could be considered that the assignment of US patent application n°12/053,015 (D3) conveyed the transfer of the priority right arising from the filing of the application, then this transfer occurred <u>after</u> the priority has been used by Pharmasset Inc. Indeed, one of the inventor, Dhanapalan Nagarathnam, executed the assignment on 31 March 2008, that is 5 days after the opposed patent was filed by claiming, *inter alia*, the priority from US patent application n°12/053,015.

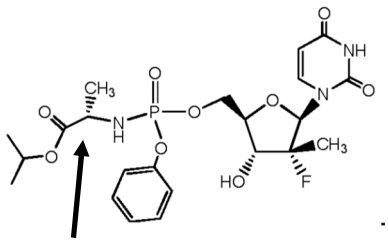
Accordingly, Pharmasset Inc. was not in full possession of this right of priority when it was claimed by it for the opposed patent and it must be considered that the right of priority from US patent application n°12/053,015 was not validly claimed.

<u>3.1.2. Claim 1 is not entitled to priority from US prov. appl. n°60/909,315</u>

3.1.2.1. The alleged support for the compound of claim 1 in US provisional 60/909,315 (first priority) is to be found in compound IX-25-2 (page 212). However, this compound is not identical to the compound of claim 1, as the stereochemistry of the asymmetric carbon linked to group R^{3b} (-CH_3) is not specified (see the arrows):



IX



Claim 1

Table IX-25.

№	R^1	R^2	R^{3a}	R^{3b}	R^4	R^5	R^6	X	Y	R^7	R^8
IX-25-2	Ph	H	H	CH_3	^{i}Pr	H	CH_3	F	OH	H	H

Similarly to what has been established previously in part **1.**, the compound of claim 1 in fact follows on from the selection within **<u>3</u>** lists of substituents or configurations:

1) Selecting one structure from the list consisting of structures II to XXXII
2) Selecting one configuration for the asymmetric carbon from the list consisting of R and S;
3) Selecting one set of substituents from the list consisting of set 1 (1-1) to set 400 (50-8).

According to the Guidelines for Examination in the EPO (November 2014 edition, Part G, Chapter VI, Paragraph 8(i)(a)), an individual chemical compound is considered as novel when it results from the selection of specific substituents from two or more “lists” of substituents given in a known generic formula.

In other words, an individual chemical compound <u>cannot</u> be considered as deriving directly and unambiguously from a generic formula when it results from the selection of specific substituents from two or more “lists” of substituents given in the generic formula.

Applied to the present case, this means that the compounds of claim 1 does not directly and unambiguously derive from priority document US provisional application n°60/909,315 (first priority).

3.1.2.2. Besides, as is recalled in the *Case Law of the Boards of Appeal of the EPO*, Seventh Edition (September 2013), Part II, Chapter D, Paragraph 2.3., the priority document must disclose the invention claimed in the subsequent application in such a way that it can be carried out by a person skilled in the art.

However, the synthesis of the compound of claim 1 is not disclosed in priority document US provisional application n°60/909,315 (first priority) and one of skill in the art is left with the undue burden of having to devise it by himself.

Accordingly, even if the transfer of the priority right arising from US provisional application n°60/909,315 (first priority) was deemed to have occurred, it follows from paragraphs 3.1.2.1. and 3.1.2.1. that claim 1 does not benefit from the priority date of 30 March 2007 and that its earliest effective date is 24 October 2007.

3.1.3. Claim 4 is not entitled to priority from US prov. appl. n°60/909,315 and n°60/982,309

Claim 4 relates to a composition comprising the compound of claim 1 and a pharmaceutically acceptable medium.

As such, the subject-matter of this claim neither derives directly and unambiguously from US provisional application n°60/909,315 (first priority).

In addition, inasmuch as claim 4 aims at protecting pharmaceutical compositions comprising the compound of claim 1, that is the first medical use of this compound, this claim is also not entitled to priority from US provisional application n°60/982,309 (second priority).

Indeed, as has been recalled previously in parts **1.** and **2.**, (i) for the priority claim to be founded the priority document must disclose the invention claimed in the subsequent application in such a way that it can be carried out by a person skilled in the art, and (ii) in case of a claimed therapeutic application, the patent must disclose the suitability of the product to be manufactured for this therapeutic application to ensure that the invention is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

However, no data are presented in either US provisional application n°60/909,315 (first priority) or US provisional application n°60/982,309 (second priority) which make it plausible that the compound of claim 1 has a therapeutic activity.

Accordingly, even if the transfer of the priority right arising from the priority applications was deemed to have occurred, claim 4 benefits neither from the priority date of 30 March 2007 nor from that of 24 October 2007 and its earliest effective date is 21 March 2008.

3.1.4. Claims 2, 3, 5 and 6 are not entitled to priority from any of the priority documents

As has been seen earlier, the subject-matter of these claims does not derive directly and unambiguously from the content of the patent as filed and is not disclosed in the patent in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

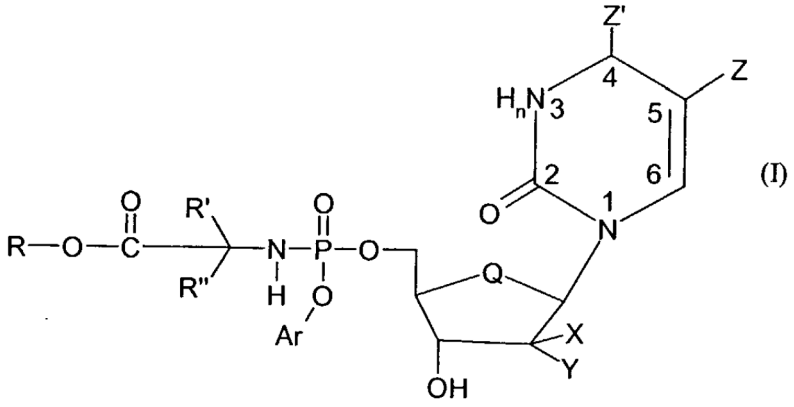
This findings are all the more true when considering the content of the priority documents which is less complete than the content of the patent.

Accordingly, even if the transfer of the priority right arising from the priority applications was deemed to have occurred, claims 2, 3, 5 and 6 are not entitled to priority from any of the priority documents and their effective date is the filing date of the patent, *i.e*. 26 March 2008.

3.2. The subject-matter of the European patent is not novel (Article 52 and 54 EPC)

International application WO 2005/012327 **(D4)** was published on 10 February 2005, *i.e.* before the earliest priority date claimed by the opposed patent (30 March 2007).

D4 discloses a compound of formula (I) (see page 3):



wherein:

R may be isopropyl (see page 7, line 20);

R' and R'' may be independently H and CH_3 (see page 8, lines 1 and 16);

Q may be O (page 3, line 21);

X and Y may be F and CH_3 (see page 3, line 22);

Ar may be phenyl (see page 5, line 29);

Z may be H (see page 3, line 26);

Z' is =O when n is 1 (see page 4, line 5).

Besides, the stereochemistry at the asymmetric center –CR'R'' corresponds to an L-amino-acid (see page 8, lines 9-10 or 19-22), *i.e.* the CH_3 group projects away from the viewer. In addition, according to the Haworth projection of the furanose cycle adopted in the above formula (I), linkage 1 project towards the viewer, 2 projects away from the viewer, 3 projects towards the viewer, one of 4 and 5 projects towards the viewer and the other projects away from the viewer.

Accordingly, D4 discloses the compound of claim 1 of the opposed patent which therefore lacks novelty.

In particular, it is submitted that the combination of specific substituents is as directly and unambiguously derived from D4 as the combination of substituents yielding the compounds of opposed claims 1 to 3 from content of the opposed patent as filed, should it be considered that these latter compounds find their support in the content of the opposed patent as filed.

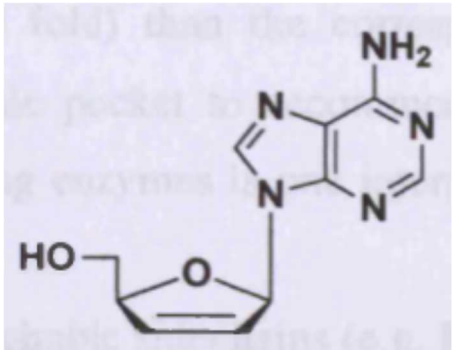
3.3. The subject-matter of the claims does not involve an inventive step (Articles 52 and 56 EPC)

3.3.1. Case where the priority right is considered not validly claimed

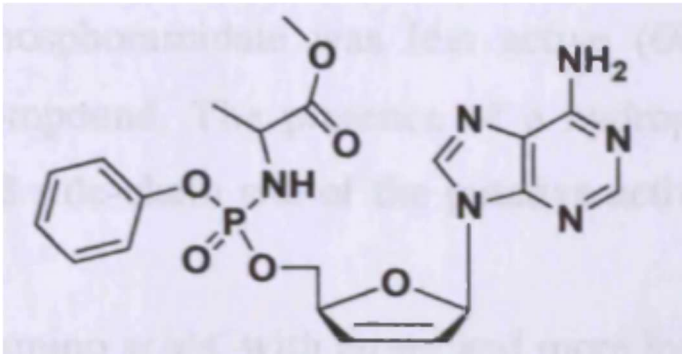
3.3.3.1. Lack of inventive step in view of D5 (or D7) as closest prior art and D6

☞ The thesis entitled "Design, Synthesis and Biological Evaluation of Novel Nucleotide Prodrugs as Potential Anti-Hepatitis C Virus Agents" **(D5)** was submitted by Plinio Perrone on February 2007, *i.e*. before the earliest priority date claimed by the opposed patent.

In Chapter 1, Perrone first recalls that there is a variety of evidence that suggests the aryl-phosphoramidate approach is the key to increasing the anti-HCV activity of modified nucleosides and mentions (i) that the phosphoramidate of d4A has shown a 1000-fold boost in activity in HIV-2 CEM cells compared to the parent nucleoside[2] and (ii) that the same parent nucleoside is inactive against Hepatitis B virus while the phosphoramidate is active at sub-µM levels (see paragraph 1.7.3. on pages 22-23).

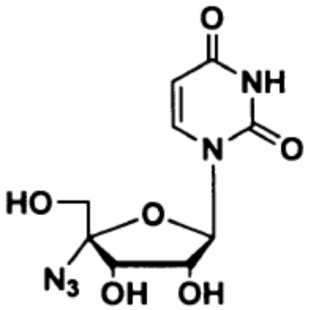


d4A (parent nucleoside)



d4A phosphoramidate

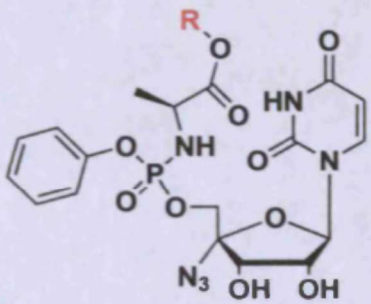
In Chapter 4, on page 78, Perrone reports that "*4'-Azidouridine (24) was tested against HCV in the replicon assay and was found completely inactive, whereas the corresponding 5'-triphosphate had an activity at 0.22 µM against RdRp [i.e. HCV NS5B]. The activity of 4'-Azidouridine triphosphate and the inactivity of the corresponding nucleoside might indicate that 4'-azidouridine (24) is poorly phosphorylated by the kinases (see Chapter One). One possibility to overcome this problem was the delivery into the cell of corresponding 5'-monophosphate via phosphoramidate technology.*"



AZU (24)

[2] See **D11** for review

On page 86, Perrone reports that L-alanine phosphoramidates of 4'-azidouridine with different substituents were prepared to explore the SAR [Structure Activity Relationship] in the ester position. The biological activity of the L-alanine phosphoramidates in the HCV replicon assay are presented in Table 4.7:



R= Ester

Cpd no.	Esters	EC_{50} (μM)	CC_{50} (μM)
121	butyl	1.2	>100
148	methyl	2.5	>100
149	ethyl	1.3	>100
150	isopropyl	0.96	>100
151	*tert*-butyl	5.1	>100
152	benzyl	0.61	>100
24	4'-azidouridine	>100	>100
5'-triphosphate-AZU= 0.22 μM IC_{50}			

Table 4.7. Biological data of L-alanine AZU phenyl phosphoramidates
EC_{50}= The concentration of phosphoramidate which produces the 50% of the maximum possible effect
CC_{50}= The concentration of phosphoramidate which produces the 50% of the maximum toxic effect

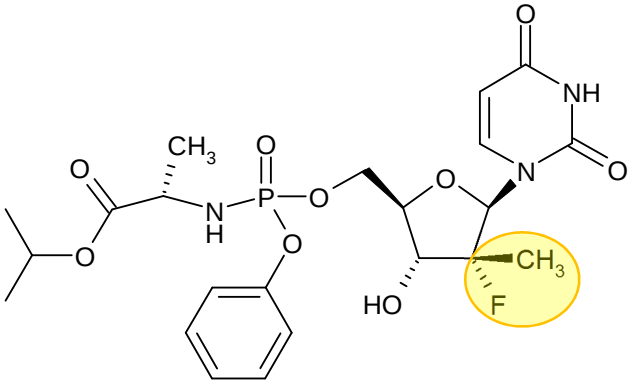
It can be seen that when R = isopropyl (compound 150), a submicromolar inhibitory effect (EC_{50}) in the HCV replicon assay is obtained. Perrone notes that methyl, ethyl and isopropyl derivatives did not show a significant difference in potency (see page 87).

On page 83, Perrone shows the phosphorochloridates (see formula below) used to prepare the L-alanine phosphoramidates of 4'-azidouridine, among which there is compound 130 with R = L-alanine and R' = isopropyl.

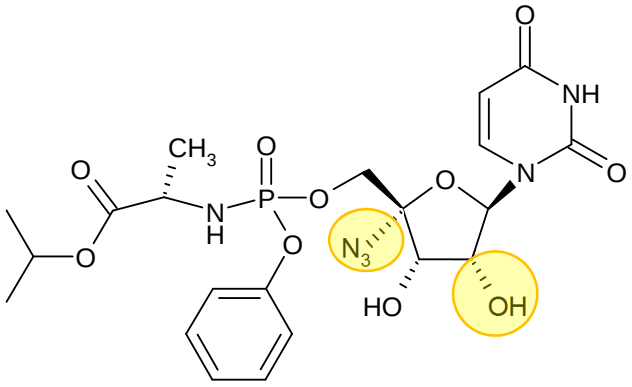
R= Amino acid
R'= Ester

☞ D5 aims at solving the same general technical problem as the opposed patent, namely providing nucleoside inhibitors of HCV NS5B and provides nucleoside phosphoramidates with a strong structural resemblance with the compounds claimed by the opposed patent. D5 may therefore qualify as a closest prior art document according to the problem and solution approach.

The difference between compound 150 of D2 and the compound of claim 1 of the opposed patent is that a N_3 group and a hydroxyl group are respectively present in the C4' and C2' positions of the 4'-azidouridine part of compound 150 instead of a H in the C4' position and F/CH_3 in the C2' position for the β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine part of the compound of opposed claim 1.



Claim 1



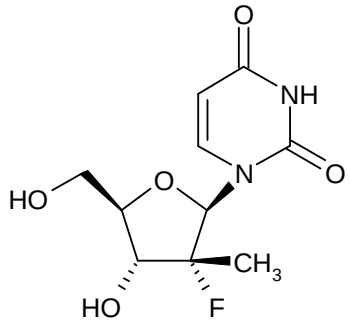
Compound 150

Both compounds present similar submicromolar inhibitory effects in the HCV replicon assay (EC50 at 0.96 µM for the compound 150 of D2 *vs*. EC90 at 0.39 for the compound of claim 1).

Accordingly, no technical effect can be associated to the difference in structure and the objective technical problem can be formulated has providing alternative anti-HCV compounds to that of D5.

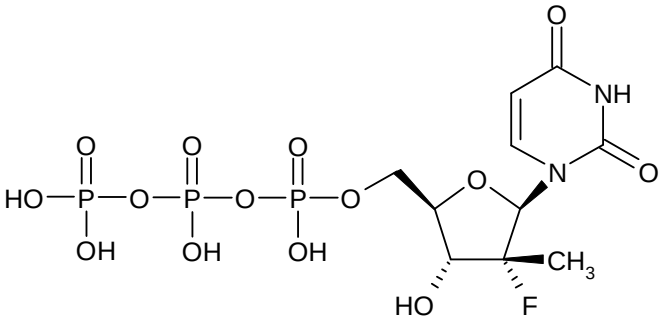
☞ The article by Ma *et al*. (2007) *J. Biol. Chem*. **282**:29812-29820 **(D6)** was published on 12 October 2007, that is between the first and second priority dates invalidly claimed by the opposed patents and before the effective date of the opposed patent.

D6 discloses that RO2433-TP (the triphosphate from of β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine, see below) is a potent inhibitor of RNA synthesis by HCV polymerase while unphopshorylated RO2433 is not active (see page 29815, right column).



RO2433

(β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine)



RO2433-TP

Citing Perrone *et al*. (2007) *J. Med. Chem.* **50**:1840-1849 **(D7)**, which disclosure is similar to the above-described Thesis (D5) by the same Perrone, D6 draws a parallel between RO2433 and 4'-azidouridine, which is inactive against HCV, but which becomes a potent inhibitor of HCV replication when delivered as a monophosphate prodrug, demonstrating that a block of monophosphate formation resulted in lack of antiviral activity of 4'-azidouridine; D6 assumes a similar block of RO2433 phosphorylation to its monophosphate RO2433-MP (see page 29819, left column), which prevents the subsequent phosphorylation to RO2433-DP and RO2433-TP (see figure 7, page 29819).

In addition, D6 notes that the longer intracellular half-life of RO2433-TP as compared to PSI-6130-TP (the cytidine analogue of RO2433-TP, then undergoing clinical development) (38 h *vs*. 4.7 h) may have pharmacological relevance for maintaining more constant concentrations of the antiviral triphosphate over the dosing period in clinical studies.

☞ One of skill in the art wishing to solve the objective technical problem would have been prompted to replace 4'-azidouridine by β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine in the compound 150 of D5, thereby arriving at the compound of claim 1, as he would have expected this would allow overcoming the block of phosphorylation of RO2433, thereby inhibiting HCV replication and leading to the clinically advantageous RO2433-TP.

Accordingly, the subject-matter of claims 1 and 4 lacks an inventive step.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture does not involve an inventive step. Therefore the subject-matter of claims 2, 3, 5 and 6 also lack an inventive step.

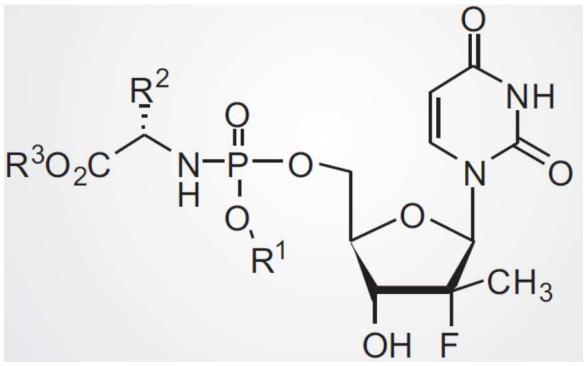
It should be noted that a similar reasoning can be followed by using D7 (published online on 12 March 2007, *i.e*. before the first priority date) instead of D5, in view of their similar content.

3.3.3.2. Lack of inventive step in view of D5 (or D7) as closest prior art and D8

D8 is a poster presented at the 14th International Symposium on Hepatitis C Virus and Related Viruses which was held in Glasgow (Scotland) on 9-13 September 2007, *i.e*. between the first and second invalidly claimed priority dates.

It should be noted that a poster and a presentation with a similar content were also made public at the 2nd International Workshop held in Boston on October 31, 2007 (between the second and third invalidly claimed priority dates).

D8 discloses the β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine phophoramidate compound PSI-6206 having the following formula:



PSI-6206

D8 further discloses that β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine phophoramidates are potent inhibitors of HCV and that they have potential as therapeutic agents for the treatment of HCV. D8 also shows that variants at the R^1, R^2 or R^3 positions exhibit a strong inhibitory activity in the HCV replicon assay.

☞ Thus, one of skill in the art wishing to solve the objective technical problem previously defined using D5 as closest prior art, namely providing alternative anti-HCV compounds to that of D5, would have been incited to replace the 4'-azidouridine part of compound 150 of D5 by the β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine part of PSI-6206, thereby arriving at the compound of claim 1, as he would have expected this compound to be an anti-HCV compound in view of D8 which discloses that phosphoramidates of β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine are potent inhibitors of HCV.

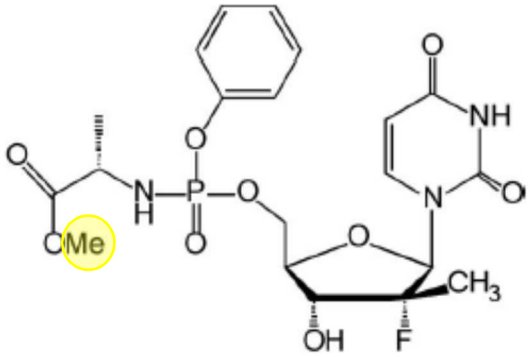
Accordingly, the subject-matter of claims 1 and 4 lacks an inventive step.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture does not involve an inventive step. Therefore the subject-matter of claims 2, 3, 5 and 6 also lack an inventive step.

Here again, it should be noted that a similar reasoning can be followed by using D7 instead of D5.

3.3.3.3. Lack of inventive step in view of D9 as closest prior art and D5 (or D7)

Murakami *et al*. (2008) *Antimicrob. Agents Chemother*. **52**:458-464 **(D9)** show that PSI-7672 (see below) a phosphoramidate of β-D-2'-deoxy-2'-fluoro-2'-C-methyluridine has an anti-HCV replicon activity of 1.6 µM (EC_{90}, see Table 2 on page 461).



PSI-7672

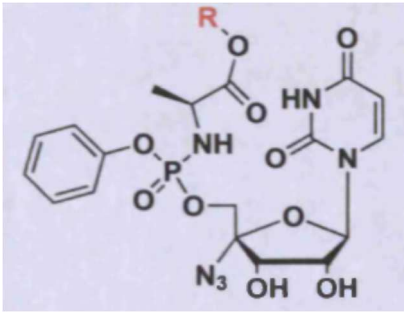
D9 solves the same general technical problem as the opposed patent, namely providing nucleoside inhibitors of HCV RNA polymerase and provides nucleoside phosphoramidates

with a strong structural resemblance with the compounds claimed by the opposed patent. D9 may therefore qualify as a closest prior art document according to the problem and solution approach.

The difference between PSI-7672 and the compound of claim 1 lies in the group esterified to the carboxyl group, a methyl for PSI-7672 (circled above) and an isopropyl for the compound of claim 1.

Both compounds present similar inhibitory effects in the HCV replicon assay. Accordingly, no technical effect can be associated to the difference in structure and the objective technical problem can be formulated has providing alternative anti-HCV compounds to that of D9.

☞ One of skill in the art wishing to solve the above objective technical problem would be prompted to change the methyl group by an isopropyl group, thereby arriving at the compound of opposed claim 1, in view of D5 which teaches that methyl, ethyl and isopropyl derivatives at the R position of the following structure did not show a significant difference in potency (see page 87):



Accordingly, the subject-matter of claims 1 and 4 lacks an inventive step.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture does not involve an inventive step. Therefore the subject-matter of claims 2, 3, 5 and 6 also lack an inventive step.

Once more, it should be noted that a similar reasoning can be followed by using D7 instead of D5.

3.3.2. Case where the priority right is considered validly claimed

3.3.2.1. Lack of inventive step in view of D4

Should the subject-matter of the claims be considered novel over D4, we submit it does not involve any inventive-step in view of this same document.

According to the established jurisprudence of the board of appeals, the assessment of inventive step is to be made at the effective date of the patent on the basis of the information in the patent together with the common technical knowledge then available to the skilled person (see *Case Law of the Boards of Appeal of the EPO*, Seventh Edition (September 2013), Part I, Chapter D, Paragraph 4.6).

However, at the earliest priority dates claimed by the opposed patent (30/03/2007 and 29/10/2007), the compounds of opposed claims 1-3 are neither described as having nor shown to possess any advantageous properties not possessed by the prior art examples. This is evidenced from pages 621-622 of priority document US provisional application n° 60/909,315 (first priority) and pages 10-11 of priority document US provisional application n°60/982,309 (second priority), which report the anti-HCV effect of some compounds and make no mention of the compounds of opposed claims 1-3.

Accordingly, as is illustrated by the Guidelines for Examination in the EPO (November 2014 edition), Part G, chapter VII, Annex, paragraph 3.1(iv), the claimed invention consists merely in selecting particular chemical compounds from a broader field, *i.e*. the claimed compounds are an obvious and consequently non-inventive selection among a number of known possibilities.

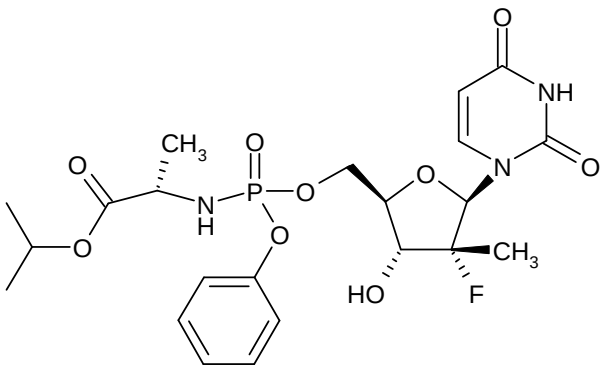
The same reasoning directly applies to the subject-matter of claims 4 to 6.

Thus, the claimed subject-matter of the opposed patent does not involve an inventive step.

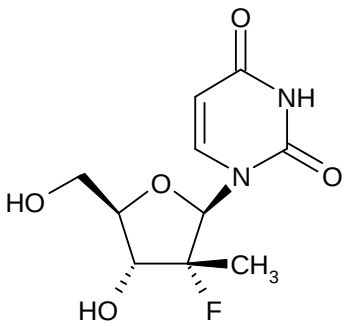
3.3.2.2. Lack of inventive step in view of D10 as closest prior art and D5 (or D7)

Clark *et al*. (2005) *J. Med. Chem*. **48**:5504-5508 **(D10)** disclose the pyrimidine nucleoside analogue 2'-deoxy-2'-fluoro-2'-C-methyluridine (see below), referred to as compound 9, and tests its anti-HCV activity (see page 5506, left column). The compound is found inactive in the HCV replicon assay (see Table 2, line of compound 9).

D10 aims at solving the same general technical problem as the opposed patent, namely providing nucleoside inhibitors of HCV replication and provides a nucleoside identical to the nucleoside part of the compounds claimed by the opposed patent. D10 may therefore qualify as a closest prior art document according to the problem and solution approach.



Compound of opposed claim 1



Compound 9 of D10

The difference between the compound of opposed claim 1 and compound 9 of D10 lies in the presence of a phosphoramidate arm in the compound of opposed claim 1. The effect of this difference is that the compound of claim 1 is active against HCV.

The objective technical problem can thus be formulated as modifying the compound 9 of D10 to make active against HCV.

D5 mentions that phosphoramidate modifications of inactive nucleoside analogs has made them active antiviral compounds (see paragraph 1.7.3. on pages 22-23). This is particularly the case of an anti-HCV uridine analog (see Table 4.7. on page 86) which is rendered active by exactly the same phosphoramidate as that of the compound of opposed claim 1 (compound 150 in Table 4.7.).

Accordingly, one of skill in the art wishing to solve the objective technical problem would have been prompted to modify compound 9 of D10 by adding a phosphoramidate moiety, in particular with the phosphoramidate moiety of compound 150 of D5, which is one of the most active anti-HCV derivative of the uridine analog tested in D5, thereby arriving at the compound of claim 1 of the opposed patent.

Accordingly, the subject-matter of claims 1 and 4 lacks an inventive step.

Besides, it is generally recognized that in the field of pharmaceuticals, separating the various stereoisomers of a racemic mixture does not involve an inventive step. Therefore the subject-matter of claims 2, 3, 5 and 6 also lack an inventive step.

It should be noted that a similar reasoning can be followed by using D7 instead of D5.