GRUPO DE TRABALHO SOBRE PROPRIEDADE INTELECTUAL

GTPI

ABIA

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS

ILUSTRÍSSIMA SENHORA DIRETORA DE PATENTES DO INSTITUTO NACIONAL DA PROPRIEDADE INDUSTRIAL

Processo: PI0410846-9
Data de depósito no Brasil: 21.04.2004
Prioridade: US 60/474,368 – 30.05.2003
Título: Nucleosídeo, seu método de síntese e composição farmacêutica
Depositante: GILEAD PHARMASSET LLC (US).

ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS – ABIA e outros, doravante Requerentes, já qualificados nos autos do processo em epígrafe, vem respeitosamente à presença de Vossa Senhoria, apresentar a presente

COMPLEMENTAÇAO AO SUBSÍDIO AO EXAME TÉCNICO

referente ao pedido de patente de invenção PI0410846-9, depositado por Gilead Pharmasset LLC, na qual apresenta **argumentos complementares** ao subsídio ao exame técnico apresentado em 15 de maio de 2015 (petição 020150009402) e complementações apresentada em 29 de julho de 2016 (petição 020160004842) e em 26 de junho de 2018 (petição 870180054896), os quais reforçam as razões de **INDEFERIMENTO do referido pedido de patente** por **ausência** de cumprimento dos requisitos e condições legais de patenteabilidade, especialmente **atividade inventiva** (artigos 8º e 13 da Lei nº 9.279/1996 - LPI), **aplicação industrial** (artigos 8 e 15 da LPI) e **suficiência descritiva** (artigos 24 e 25 da LPI).

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I. CONSIDERAÇÕES INICIAIS

O pedido de patente **PI0410846-9** (WO 2005/003147) entrou na fase nacional do PCT no Brasil em 30/11/2005, reivindicando a prioridade US 60/474,368 de 30/05/2003. Ao longo do exame técnico, a depositante alterou o quadro reivindicatório (QR) sete vezes, além de modificar o título alegando melhor adequação com matéria pleiteada (Quadro 1).

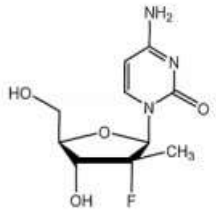
Quadro 1: Alterações do QR do **PI0410846-9**

Petição	Data	Título	Quadro reivindicatório
020050139056	30/11/2005	Composto, composição e usos para o tratamento de uma infecção por *Flaviviridae*	126 reivindicações
020070050057	19/04/2007	Composto, composição e usos para o tratamento de uma infecção por *Flaviviridae*	130 reivindicações
00120005531	23/01/2012	Nucleosídeo, composição farmacêutica, método de síntese do nucleosídeo e composição lipossomal	19 reivindicações
860150232689	08/10/2015	Nucleosídeo e método de síntese	16 reivindicações
870160021605	20/05/2016	Nucleosídeo, seu método de síntese e composição farmacêutica	13 reivindicações (QR “pendente”)
870170096785	11/12/2017	Nucleosídeos e composições farmacêuticas para o tratamento de uma infecção por *Flaviviridae*, e método de síntese de nucleosídeo	7 reivindicações (QR “auxiliar”)
870180061311	16/07/2018	Nucleosídeo e composição farmacêutica compreendendo o mesmo	2 reivindicações

O atual QR proposto pela depositante possui apenas duas reivindicações, que são referentes ao composto base (2’R)-2’-desoxi-2’-fluor-2’-C-metilcitidina e uma composição com esse composto base. Segue abaixo o QR (Figura 1).

REIVINDICAÇÕES

1. Nucleosídeo ou o sal farmaceuticamente aceitável deste, **caracterizado** por ser o (2'R)-2'-desoxi-2'-fluor-2'-C-metil nucleosídeo (β-D) da fórmula:



2. Composição farmacêutica, **caracterizada** pelo fato de compreender um nucleosídeo definido na reivindicação 1, ou o sal farmaceuticamente aceitável do mesmo, e um veículo farmaceuticamente aceitável.

Figura 1: Reivindicações pendentes do **PI0410846-9**

Esse composto base (PSI-6130) apresenta o nucleosídeo citidina (base nitrogenada citosina), diferentemente do composto base do sofosbuvir, que apresenta a uridina (base uracila) e que precisa ser fosforilado para ter atividade. Portanto, a restrição do escopo para a base citosina não protege a base nucleosídica do sofosbuvir, que é o produto atualmente no mercado.

II. SOBRE O EFEITO TÉCNICO INESPERADO

As duas reivindicações que ficaram no último quadro reivindicatório do **PI0410846-9** se sustentam pela alegação da depositante de um "efeito técnico inesperado" do composto (2'R)-2'-desoxi-2'-fluor-2'-C-metilcitidina, por conta de maior atividade anti-HCV e menor toxicidade em comparação com os compostos 2'-C-metilcitidina e 2'-C-metiladenosina, que seria o problema técnico a ser resolvido.

Nos subsídios anteriores, foi apresentada uma série de anterioridades[1] sobre a falta de atividade inventiva do composto reivindicado (com base citosina), a partir do entendimento de que é óbvio para um técnico no assunto fazer algumas substituições a partir do conhecimento disponível no estado da técnica à época e chegar a esse composto. Contudo, o entendimento do último parecer técnico do INPI considerou que o "efeito técnico inesperado", alegado pela depositante, invalidaria a alegação de falta de atividade inventiva.

Primeiramente, gostaríamos de reforçar a argumentação presente no subsídio de Farmanguinhos, apresentado em 07 de agosto de 2018. Isto porque o relatório descritivo do pedido ora em exame deixa evidente que a **performance dos compostos de citidina ora reivindicados é semelhante, ou até menos potente, do que a dos outros compostos do estado da técnica** usados a título de comparação (revelados em WO01/90121). O mesmo ocorre em relação à toxicidade, restando evidente que **o composto ora reivindicado está na mesma faixa de citotoxicidade dos outros compostos já revelados no estado da técnica** com os quais foi comparado.

Outro aspecto importante é que esse composto reivindicado (derivado da citidina) não age no organismo, é inativo terapeuticamente, ele é apenas um intermediário da primeira rota de síntese do sofosbuvir (derivado da uridina), pró-fármaco que dá origem à forma ativa no organismo, como demonstra a Figura 2.

[1] WO02/57425. Título: Nucleoside derivatives as inhibitors of RNA-dependent RNA viral polymerase. Depositantes: Isis Pharmaceuticals, INC. (US) / Merck Sharp & Dohme Corp. (US). Data de depósito: 18/01/2002. Correspondente brasileira: PI0206614-9.
WO01/90121. Título: Methods and compositions for treating hepatitis c vírus. Depositante: Novirio Pharmaceuticals Limited,; Universita Degli Studi Di Cagliari,; Sommadossi, Jean-Pierre,; Lacolla, Paulo. Data de depósito: 29/11/2001. Correspondente brasileira: PI0111127-2
WO99/43691. Título: 2`-fluoronucleoside. Depositante: Mory University (US) / The University of Georgia Research Foundation, Inc. (US). Data de depósito: 25/02/1999. Correspondente brasileira: PI9908270-5 A2.
Pankiewicz, K.W. "Fluorination nucleosides" - Carbohydrate Reasearch 327, 87-105, 2000.
Carroll, Steven S. et al., Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs, The Journal of Biological, 27 January 2003.

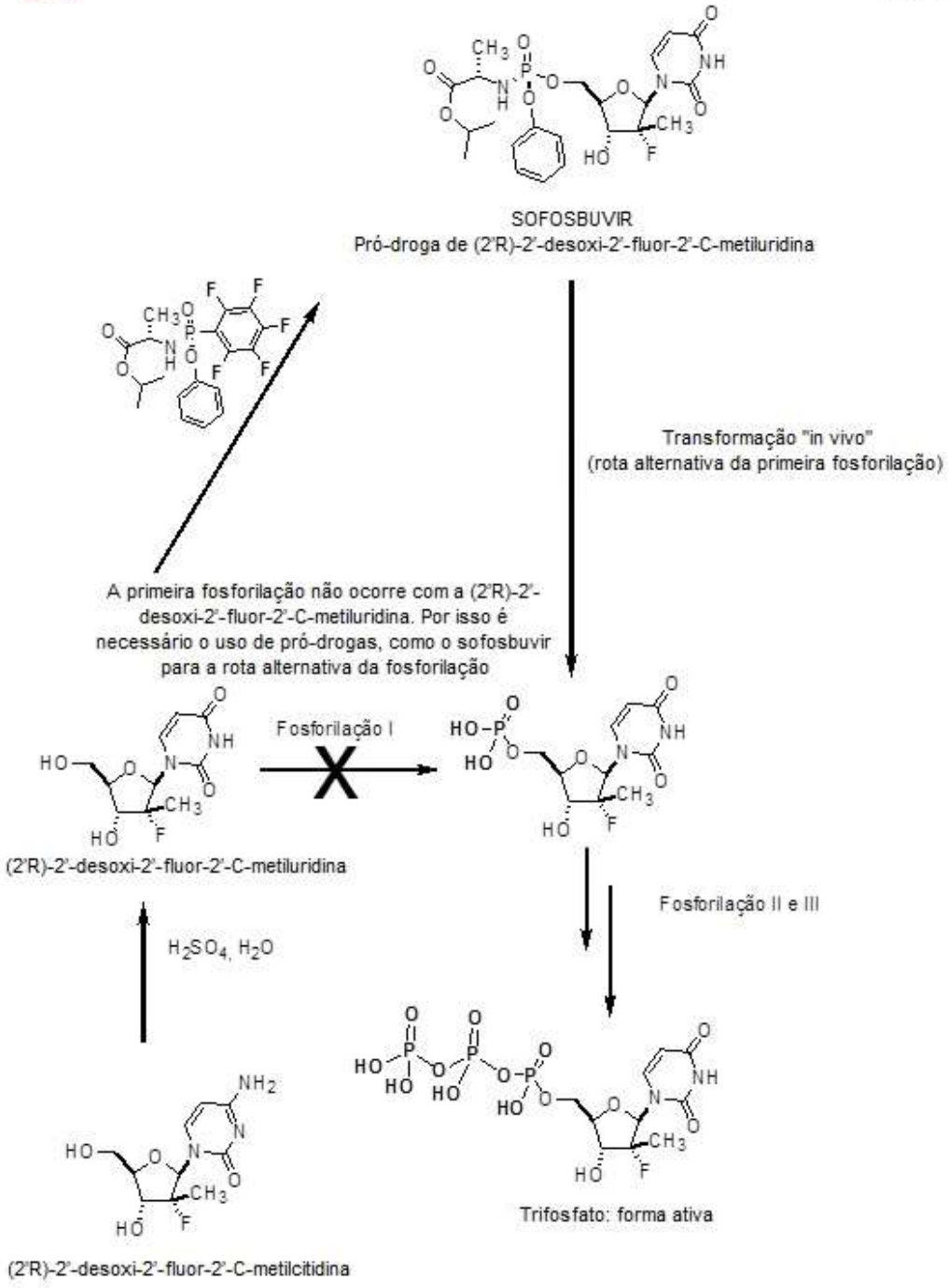


Figura 2: Rota de síntese e transformações do sofosbuvir para chegar à forma ativa

Para produzir o efeito inibitório no vírus HCV, os compostos análogos de nucleosídeos precisam ser convertidos no organismo, por processos de metabolização, na forma ativa trifosfato, dando origem a compostos análogos de nucleotídeos. A primeira fosforilação é a mais importante, já que uma vez ocorrida, as outras ocorrem facilmente. Como a primeira fosforilação não ocorre com a (2'R)-2'-desoxi-2'-fluor-2'-C-metiluridina, foi desenvolvido o sofosbuvir, que é um pró-fármaco do composto (2'R)-2'-desoxi-2'-fluor-2'-C-metiluridina.

No entanto, **não é automática a extrapolação dos resultados de atividade anti-HCV e toxicidade do intermediário para o composto que de fato atua no organismo**. Dessa forma, ainda que houvesse um suposto efeito técnico inesperado de atividade anti-HCV e toxicidade para o composto com base citosina reivindicado, tal efeito **não teria relevância prática, ou seja, aplicação industrial**, já que o efeito técnico inesperado só é importante quando se fala sobre a atividade e toxicidade do produto que entra em contato com o organismo.

Não por outra razão, o desenvolvimento do composto em questão foi abandonado enquanto possível solução para o problema técnico que pretendia resolver, conforme afirma Furman[2] *et al* (2011):

> No entanto, foi demonstrado que quando o PSI-6130 foi administrado oralmente, uma certa porcentagem foi metabolizada no derivado de uridina inativo [19]. Estudos bioquímicos revelaram que o PSI-6130 foi desaminado ao congénere da uridina pela citidina-desaminase humana [19]. Para agravar a questão, a biodisponibilidade oral do PSI-6130 foi determinada como sendo inferior a 25%. A baixa biodisponibilidade em conjunção com a produção de um metabólito inativo apresentou desafios significativos para alcançar níveis terapêuticos suficientes do fármaco ativo (Furman[3] *et al*, 2011, p. 310, tradução livre).

[2] Furman esteve envolvido no desenvolvimento de PSI-6130.
[3] Furman, P. A.; Otto, M. J.; Sofia, M. J. Discovery and development of PSI-6130/RG7128. Antiviral Drugs: From Basic Discovery through Clinical Trials, 2011.

Além disso, Vere Hodge (2015) relata o seguinte de Furman *et al* (2011):

> No entanto, PSI-6130 foi pouco absorvido por via oral e houve conversão significativa para o análogo da uridina inativa. Uma abordagem pró-fármaco, em colaboração com a Roche, resultou no RG-7128 que aumentou a biodisponibilidade do PSI-6130 em cinco vezes, mas não foi uma abordagem que pudesse aumentar a meia-vida curta do PSI-6130-TP (T1/2 = 5 h). (Vere Hodge[4], 2015, p. 174, tradução livre).

Como tal, mesmo o pró-fármaco do PSI-6130 (RG-7128), composto coberto pelas duas reivindicações que ainda restam no presente pedido de patentes, não foi considerado suficientemente ativo e o seu desenvolvimento foi interrompido.

Desta forma, a partir de todo o revelado nos diversos subsídios apresentados e nessa complementação, e tendo como base o estabelecido nas Diretrizes de Exame de Pedidos de Patente – Bloco II – Patenteabilidade e na Lei n° 9279/1996, fica óbvio que as reivindicações 1 e 2 **carecem de atividade inventiva, aplicação industrial e suficiência descritiva**. Portanto, **não merecem ser deferidas por não atenderem aos artigos 8°, 13, 15, 24 e 25 da LPI**.

III. ANTERIORIDADES E OPINIÃO TÉCNICA SOBRE FALTA DE SUFICIENCIA DESCRITIVA E ATIVIDADE INVENTIVA

A seguir reproduzimos na íntegra opinião técnica do especialista Dr. Anand Grover[5], advogado sênior e ex-relator especial das Nações Unidas sobre o direito à saúde física e mental, a respeito do atual QR do **PI0410846-9**. O Dr. Anand Grover apresenta argumentos de **falta de suficiência descritiva e atividade inventiva** de acordo com o estabelecido nas diretrizes de exame do INPI e com base em anterioridades, algumas das quais inéditas neste exame, as quais as Requerentes

[4] Vere Hodge, R. A. Meeting report: 28th International Conference on Antiviral Research in Rome, Italy. Antiviral Research 123, p. 172–187, 2015.
[5] O anexo 13 é uma apresentação do especialista Dr. Anand Grover.

solicitam que sejam consideradas por este INPI no processo de análise do pedido de patente ora em tela.

Nesta opinião técnica também são comentados alguns elementos apresentados pela depositante em sua última manifestação como a declaração do Dr. Stanislaw Wnuk, apresentada durante a oposição na Índia, e o caso envolvendo a empresa Idenix nos EUA. A versão original assinada da opinião técnica do Dr. Anand Grover também compõe este subsídio como Anexo 12.

Anterioridades apresentadas:

- **(inédita)** Meijer, A. Development of a novel promoter system for thioglycoside activation and its application in the synthesis of a GD3 bis-lactam. Lund University, 2003.
- WO 2001/90121. Publicado em: 29 de novembro de 2001.
- WO 2002/057425. Publicado em: 25 de julho de 2002.
- **(inédita)** Matsuda et al. Radical Deoxygenation of Ter-Alcohols in 2'-branched-chian-sugar pyrimidine nucleosides: synthesis and antileukemic activity of 2'-deoxy-2'(S)-methylcytidine, 1987.
- **(inédita)** Park, B. K.; Kitteringham, N. R. Effects of Fluorine Substitution on Drug Metabolism: Pharmacological and Toxicological Implications. Drug Metabolism Reviews, 26(3), 605-643, 1994.
- Pankiewicz, K. W. Fluorinated Nucleosides. Carbohydrate Research 327, 87-105, 2000.
- **(inédita)** Middleton, W. J. New Flourinating Reagents, Dialkylaminosulfur Fluorides, 1975.
- WO 1999/43691. Publicado em: 02 de setembro de 1999.
- WO 2002/057287. Publicado em: 25 de julho de 2002.

Technical opinion

August 30, 2018

Mr. Felipe Carvalho, of Medicine Sans Frontieres (MSF), the Querist approached me with the following query in relation to patent application no. PI 0410846-9A, filed before the INPI at Brazil, viz.:

- With regard to sufficient disclosure to what extent may disclosure related to glycosylation reaction matters be relied on?
- How can the argument of Dr. Stanislaw Wnuk which was submitted during the patent prosecution in India, that the descriptive report sufficiently describes a method to obtain the claimed compound, be countered?
- What is the closest prior art that may be relied on?
- How can the INPI's interpretation of Markush-based prior art and "unexpected technical effect" be challenged?
- Is there is any data that shows that other compounds disclosed in the descriptive report would also have high specificity, potency and less toxicity?

FACTS

1. Gilead Sciences, Inc. has filed a patent application in Brazil which covers the Active Pharmaceutical Compound of Sofosbuvir, viz. β-D (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine.
2. The objections raised by the INPI and the response from Gilead is listed below in tabular form:

Requirement	1st exam by INPI (rejection) 09/2017	Response by Gilead 12/2017	Response by INPI (partial grant)	Last response by Gilead

			04/2018	07/2018
Sufficient disclosure	The glycosylation reaction is not sufficiently disclosed especially temperatures are not specified, thus **claims 1-6** (compounds) are not valid neither **claim 7** (synthesis method)	- There is enough information in the descriptive report - the evidence used by INPI (*Li, et al., Organic Letters, v.3, n.7, pp 1025-1028*) to sustain that temperature is crucial was misunderstood	- synthesis method and pharmaceutical formulation claims removed - For **claims 1-6**, it is accepted that temperature must not be specified because it is not the only factor affecting the reaction. - Hence claim 7 was also deemed to be sufficiently disclosed - Insufficient disclosure objection was withdrawn	-To defend sufficient disclosure of remaining claims, Gilead referred to submission of Dr. Stanislaw Wnuk during the patent opposition in India, where he affirmed that the descriptive report provides sufficient information including the temperature required to obtain the claimed compound

Novelty	-Did not acknowledge the WO/2002/057425			-That Gilead prevailed in cases against Idenix, which shows that other players could not develop the same compound on the basis of the teachings in the prior art
Inventive Step	-That WO 01/90121 and WO 99/43691 made it obvious for a person skilled in the art to explore 2'-fluoro (down)-2'-C-methyl (up) for HCV treatment, thus claims 1-6 (compounds) have	-WO 01/90121 and WO 99/43691 lack data on anti-HCV activity -WO 01/90121 does not mention fluoro in position 2 -Comparative data between the patent and	-consider that Gilead demonstrated an "unexpected technical effect", thus **claim 5** –which is *(2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up)* nucleosides -	-None of the prior art shows how to synthesize the claimed (2'R)-2'-deoxy-2'-fluoro (down)-2'-C-methyl (up) nucleosides and no

	no inventive step	WO 01/90121 - additional evidence on the advantages of the compound	can be considered patentable. - Part of **claim 7** which covers a pharmaceutical formulation covering the compound is also found patentable.	references anticipated or suggested that it would be useful as specific, potent and less toxic anti-HCV treatments.

OPINION

ON INSUFFICIENT DISCLOSURE

1. The *INPI Guidelines for the Examination of Patent Applications*[6] indicates that, "3.38 *In the case of Markush claims, the examiner shall ensure that the procurement procedures described in the report substantially enable the preparation of all claimed compounds, i.e., the examples should be representative of all classes of the claimed compounds, or all of these should be sufficiently descriptive in the descriptive report.*"
2. Further, in the context of sufficient disclosure, the guidelines also mention that, "3.91 *It should be noted that although an objection of lack of reasoning is an objection under Article 25 of the IPL, it may often, as in the examples in item 3.94, also be regarded as an objection of*

[6] http://www.wipo.int/wipolex/en/text.jsp?file_id=437779

descriptive insufficiency of the invention in accordance with article 24 of the LPI (see item 2.13). In this context, the objection lies in the fact that the application as disclosed is insufficient to enable a person skilled in the art to carry out the "invention" throughout the claimed field, although sufficient in relation to a more restricted "invention". Both conditions are required to assert the principle that the wording of a claim must be substantiated in the descriptive report of the application.

3.92 It should be noted that the descriptive sufficiency of the invention must be verified only in the descriptive report, while Article 25 refers to the grounds of the claiming frame in the descriptive report."

Temperature in glycosylation reaction

3. As on the priority date of the opposed application, it was known that glycosylation reaction can be performed at almost any temperature. However pertinent to note is, "***The factors that determine at what temperature to run a glycosylation reaction are the stability and the reactivity of the components.*** *For unreactive donor/promoter systems a high reaction temperature is necessary, whereas for a more reactive system, a lower temperature is sufficient for complete activation. In general, lower temperatures suppress unwanted side reactions, like the cleavage of protective groups, often mediated by the acid formed in the condensation reaction, and reactions between the promoter system and the product or acceptor molecule.* ***The temperature can also influence the stereoselectivity of the reaction. A low temperature usually favors the equatorial kinetic product, whereas a higher temperature favors the thermodynamic axial product****." (See "Development of a novel promoter system for thioglycoside activation and its application in the*

synthesis of a GD3 bis-lactam" Andréas Meijer, Lund University, 2003, hereinafter referred as *Meijer,* at internal page 19 at section 2.7.1).

4. Therefore, while temperature *per se* may not be an important factor, it becomes important where the result requires selection of a stereoisomer. The descriptive report of the opposed application fails to identify or discuss the stability or the reactivity of the compounds. Therefore, the descriptive report falls short of enabling a person skilled in the art to arrive at the claimed compound.
5. Further, low or high temperatures only indicate whether a person skilled in the art would arrive at the equatorial kinetic or axial thermodynamic product. Simply using low or high temperature does not teach how to obtain the claimed β-D stereoisomer of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside.
6. *Meijer* also points out that protective groups used in the reaction may have stereodirective effects (See Meijer at internal page 26 at section 3.2). Further, Meijer discloses that nucleophiles may also influence the stereochemical outcome of the glycosylation (See Meijer at internal page 30 at section 3.3). Even if one is to agree with Dr. Stanislaw Wnuk's submission made before the Indian Patent Office, it is only limited to the point that the descriptive report has enough information to synthesize 2'-deoxy-2'-fluoro-2'-C-methyl nucleoside. However information in the descriptive report is insufficient to enable a person skilled in the art to obtain the particular stereoisomer, viz. the **β-D** form of (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside.
7. Therefore, the descriptive report has not provided any specific process for the preparation of the claimed **β-D** stereoisomer.

Reason for choosing compound of claim 1 has not been disclosed

8. The compound of claim 1 has been chosen arbitrarily. In fact, the descriptive report has failed to identify any potential advantage of choosing β-D (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside over β-L (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside.
9. In light of the failure to fully and particularly describe the invention, claim 1 of the opposed application must be rejected.

Activity of the claimed compound should have been disclosed in the descriptive report

10. Tables 1-8 of the descriptive report (See internal pages 118 through 121) only indicate the activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine. The descriptive report has failed to indicate the activity of the claimed β-D (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside.
11. Therefore, the answer to the first two questions posed by the querist, in my opinion is that neither of the documents indicate that the claimed stereoisomer could be obtained by the disclosed process. Hence, the descriptive report has not sufficiently disclosed the best method to obtain the claimed compound.

ON NOVELTY

12. While determining novelty, the Court looks at disclosure and enablement. That is, whether the invention that has been challenged was disclosed in prior art. Once that disclosure is established, the next question to be determined is whether the disclosure is enabled, i.e. whether an ordinarily skilled person would be able to perform the disclosed invention if she attempted to do so by the using disclosed matter and common general knowledge.

13. Further, if the prior disclosure is such that if performed, it results in the claimed/challenged patent being infringed, then it is stated to be enabled (*Synthon BV v Smithkline Beecham plc* [2005] UKHL 59]

Idenix's case against Gilead

14. Idenix's patents US 6,914,054 (US '054) and US 7,608,597 (US '597) were related to placement of a methyl group at the 2' up position of a nucleoside. In 2013, Idenix sued Gilead claiming that Gilead's Sofosbuvir (which is the claimed compound in the Present Opposition Application) infringed Gilead's US '054 and US '597 patents. The patent infringement suit was brought before the United States District Court for the District of Massachusetts and thereafter transferred to the United States District Court for the District of Delaware where the infringement claim was later limited to US '597. The jury had found Gilead to be infringing Idenix's patent US '597. However, Gilead filed a motion for declaring Idenix's US '597 as invalid for lack of enablement or written description (*Idenix Pharmaceuticals LLC and Universita Degli Studi di Cagliari v Gilead Sciences, Inc.* C.A. No.14-846-LPS hereinafter, "*Idenix v Gilead*"). Vide judgment dated 16.02.2018, the United States District Court for the District of Delaware had found that US '597 was invalid due to lack of enablement. The Court in its judgement found that US '587 disclosed fluorine as a candidate for the 2' up position and not 2' down position.
15. Therefore, in my opinion, in light of the judgment in *Idenix v Gilead,* it may be difficult to rely on US '597 for showing lack of novelty in the opposed application before the INPI. However, the judgment does indicate the features that were disclosed in US '597, and those may be used for bolstering the argument on non-obviousness, as will be discussed in the section below.

ON OBVIOUSNESS

16. With regard to the query on whether there is a "closer prior art" document- In order to establish obviousness different prior art documents have to be read in conjugation to understand what a Person Ordinarily Skilled in the Art (POSITA) could have found.
17. While determining obviousness, the Courts look at the common general knowledge in the field, whether the alleged invention was merely a matter of trial and error, and how would a person skilled in the art (POSITA) look at the documents in light of the common general knowledge (***General Tire & Rubber Company v. The Firestone Tyre and Rubber Company Limited*** (1972) R.P.C. 457)
18. While determining obviousness, the prior art documents are not to be looked at in isolation. The techniques and technologies pre-existing the invention in question may be assessed by combining or creating a mosaic of the prior art documents (Delhi High Court, India in the matter of ***Glaverbell SA vs. Dave Rose and Ors***. MANU/DE/0205/2010)
19. Further, obviousness does not require absolute predictability of success. All that is required is a reasonable expectation of success. (US Federal Court in In Re O'Farrell (853 F.2d 894) (Fed. Cir. 1988)). In fact, in certain cases, "*One of the matters which it may be appropriate to take into account is whether it was obvious to try a particular route to an improved product or process. There may be no certainty of success but the skilled person might nevertheless assess the prospects of success as being sufficient to warrant a trial. In some circumstances this may be sufficient to render an invention obvious.*" *Medimmune Ltd v Novartis Pharmaceuticals UK Ltd* [2012] EWCA Civ 1234.

20. Hence, while determining obviousness, a person skilled in the art would use together the teachings of the prior art documents. In context of the opposed application, it may be shown that as on the priority date of the application

i) Substitutions at 2' position of a nucleoside used in treatment of Hepatitis C Virus was known (as also admitted by the Applicant at (Pg. 11, line 30 of the descriptive report of the Opposed Application);

ii) Particular substitution of methyl (up) and hydroxy at 2' position of the identified nucleoside was known;

iii) It was known that fluorine and hydroxy groups are isosteres;

iv) Use of fluorine for enhanced metabolism was known and it was also known that fluorine could be introduced in the nucleoside through inter alia Diethylaminosulfur Trifluoride (DAST) process (use of DAST for fluorination is also admitted by the Applicant at internal page 96, lines 19-24 of descriptive report);

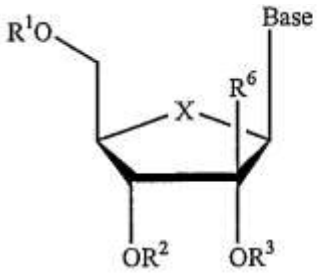
v) Particular substitution of methyl and fluorine at 2' position of the identified nucleoside in β-D and β-L configuration was known.

i) Substitutions at 2' position a nucleoside used in treatment of Hepatitis C Virus

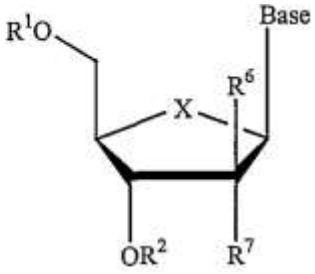
WO 01/90121 (Published: November 29, 2001)

21. WO 01/90121, titled "*Methods and Compositions for Treating Hepatitis C Virus*" ("WO '121") was published on November 29, 2001 which is earlier than the priority date of the Opposed Application.

22. WO '121 discloses "*compounds, methods and compositions for the treatment of Hepatitis C infection…that include an effective hepatitis C treatment amount of a* ***β-D or β-L nucleosides***" (internal page 7 at placitum 15-17 and internal page 17 at lines 21-22). Attention is drawn to the eighth principal embodiment with Formulas X and XI, whose structures have been reproduced below (internal page 13 of WO '121):



(X)



(XI)

Wherein:

Base is a purine or **pyrimidine base**

R^1, R^2, R^3 are independently **H**; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered

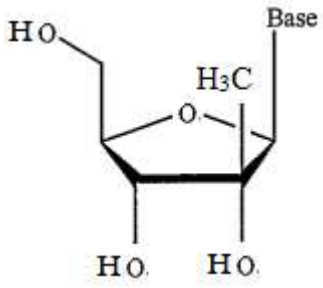
in vivo is capable of providing a compound wherein R^1, R^2, R^3 is independently H or phosphate;

R^6 is hydrogen, **hydroxy**, alkyl **(including lower alkyl)**, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl),-C(O)O(lower alkyl),-O(acyl),_O(alkyl), -O(lower alkyl), -O(alkenyl), chloro, bromo, **fluoro**, iodo, NO_2, NH_2,-NH (lower alkyl), -NH (acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 is hydrogen, OR^3, hydroxy, **alkyl (including lower alkyl)**, azido, cyano, allkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(Acyl), -O(alkyl).-O(lower alkyl),-O(alkenyl), chlorine, bromide, iodine, NO_2, NH_2,-NH(lower alkyl),-NH(acyl),-N(lower alkyl)$_2$, -N(acyl)$_2$ and

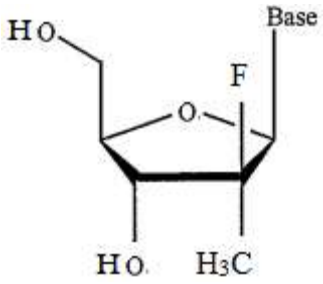
X is **O**, S, SO_2 or CH_2. (emphasis added)

23. On arranging one of the substitutions as emphasised above, wherein R^1, R^2, R^3 is H, R^6 is a lower alkyl such as methyl, and X is O on formula X, the following compound is obtained:



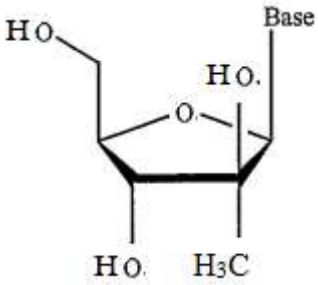
Formula A

24. Another arrangement with the substitutes on Formula XI, wherein R^1, R^2 is H, R^6 is fluoro and R^7 is a lower alkyl such methyl and X is O yields the following compound:



Formula B

25. Another combination of substitutes on compound XI wherein R^1, R^2 is H, R^6 is hydroxy and R^7 is a lower alkyl such methyl and X is O yields the following compound:



Formula C

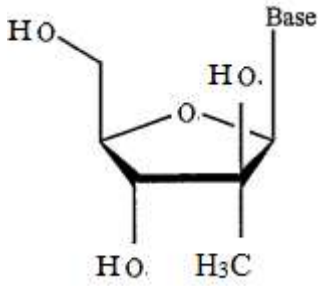
26. Further, WO '121 also discloses substitution of chlorine, bromide and iodine at R^7. Given that the other four halogens have not been identified, a person having ordinary skill in the art, exploring alternate treatment for HCV would be motivated to also experiment with the other four halogens, including fluorine at the R^7 position.

27. WO '121 Application discloses at least 18 formulae with different substitutions at the 2' position of the nucleoside. Therefore, a person skilled in the art would be motivated to try these substitutions and their obvious alternatives to find another compound that may show similar or better activity against HCV.

28. Even in absence of values of activity of the claimed compounds in WO '121, a POSITA working on HCV drugs, on reading WO '121 would be motivated to evaluate the *in vitro* activity of the disclosed compounds.

ii) Substitution of methyl and hydroxy at 2' position of the identified nucleoside was known

29. The substitutions on Formula XI disclosed in WO '121 also disclosed substitution of hydroxy and methyl group at the 2' position of the nucleoside. Hence WO '121 also taught and disclosed hydroxy and methyl substitution at the 2' position of the nucleoside. Formula XI with substitutions at the 2' position is reproduced below:



Formula C

WO 2002/057425 (Published: July 25, 2002)

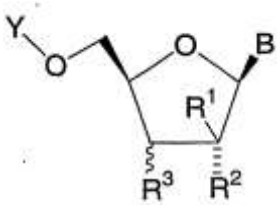
30. WO '425 is the PCT application of Idenix's US '597 application.

31. In the *Idenix v Gilead*, while the District Court of Delaware did hold Idenix's US '597 was invalid, it indicated some features that were disclosed in the patent specification. The Court recognised that Idenix's patent addressed the placement of a methyl group at the 2' up position of a nucleoside (See *Idenix v Gilead* at internal page 3, Para 1). The Court noted that, "…*the accused embodiment-2' methyl up 2' fluoro*

down-which, undisputedly, comes within the claims as construed (see,e.g.,D.I. 516 at 13), is not expressly disclosed in the '597 patent. While fluorine is disclosed as candidate for the 2' up position, it is not disclosed as a candidate for the 2' down position…Notably, fluorine is a halogen, and other halogens are disclosed as candidates for the 2' position, but, again, fluorine is not." (See *Idenix v Gilead* at internal page 21, last para)

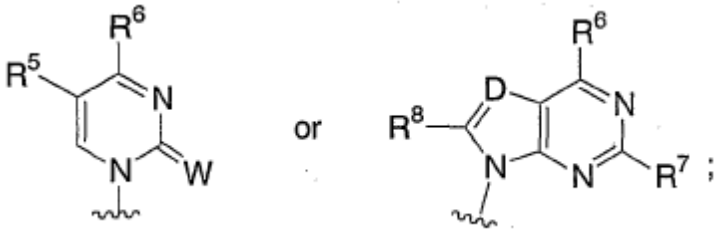
32. That is, the Court did recognise the following features were disclosed in US '597:
    a. Placement of methyl group at 2'-up position of a nucleoside;
    b. Fluorine is disclosed as a candidate for the 2' up position and not 2' down position.

33. WO '425 discloses Formula III as reproduced below (internal page 17):



(III)

wherein **B is**



;

D is N, CH, C-CN, C-NO_2, C-C_{1-3} alkyl, C-$NHCONH_2$, C-$CONR^{11}R^{11}$, C $CSNR^{11}R^{11}$, C-$COOR^{11}$, C-hydroxy, C-C_{1-3} alkoxy, C-amino, C-C_{1-4} alkylamino, C-di(C_{1-4} alkyl) amino, C-halogen, C-(1,3-thiazol-2-yl), or C-(imidazol-2-yl); wherein alkyl is unsubstituted or substituted with

one to three groups independently selected from halogen, amino, hydroxyl, carboxy, and C_{1-3} alkoxy;

W is O or S;

Y is H, C_{1-10} alkylcarbonyl, $P_3O_9H_4$, $P_2O_6H_3$, or $P(O)R^9R^{10}$;

R^1 is hydrogen, CF_3, or **C_{1-4} alkyl** and one of R^2 and R^3 is OH or C_1 alkoxy and the other of **R^2 and R^3 is selected from** the group consisting of hydrogen, **hydroxy**, **fluoro,** C_{1-3} alkyl, Trifluoromethyl, C_{1-8} alkylcarbonyloxy, C_{1-3} alkoxy; or Amino; or

R^2 is hydrogen, CF_3, or C_{1-4} alkyl and one of R^1 and R^3 is OH or C_{1-4} alkoxy and the other of R^1 and R^3 is selected from the group consisting of hydrogen, hydroxyl, fluoro, C_{1-3} alkyl, trifluoromethyl, C_{1-8} alkylcarbonyloxy, C_{1-3} alkoxy, and amino; or

R^1 and R^2 together with the carbon atom to which they are attached form a 3- to 6- membered saturated monocyclic ring optionally containing a heteroatom selected from O, S, and NC_{0-4} alkyl;

R^6 is H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl) amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, or halogen;

R_7 is hydrogen, amino, C_{1-4} alkylamino, C_{3-6} cycloalkylamino, or Di(C_{1-4} alkyl)amino;

Each R^{11} is independently H or C_{1-6} alkyl;

R^8 is H, halogen, CN, carboxy, C_{1-4} alkyloxycarbonyl, N_3, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, hydroxyl, C_{1-6} alkoxy, C_{1-6} alkyl thio, C_{1-6} alkylsulfonyl, or (C_{1-4} alkyl) $_{0-2}$ aminomethyl; and

R^9 and R^{10} are each independently hydroxyl, $OCH_2CH_2SC(=O)$t- butyl, or $OCH_2O(C=O)$iPr;

with the provisos that (a) when R^1 is hydrogen and R^2 is fluoro, then R^3 is not hydrogen, trifluoromethyl, fluoro, C_{1-3} alkyl, amino, or C_{1-3}

alkoxy; (b) when R^1 is hydrogen and R^2 is fluoro, hydroxyl, or C_{1-3} alkoxy, then R^3 is not hydrogen or fluoro; and when R^1 is hydrogen and R^2 is hydroxyl, then R^3 is not β-hydroxy.

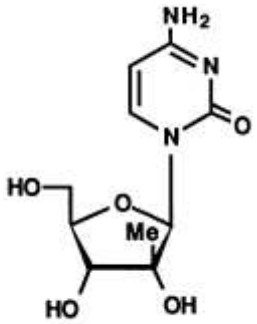
34. WO '425 also discloses substitution of **C_{1-4}** alkyl (which includes methyl) at R^1 and **hydroxyl** at R^2.

35. WO '425 also describes the assays employed to measure the inhibition of HCV NS5B polymerase and HCV replication. In the assays used on representative compounds, the HCV NS5B polymerase assay exhibited IC_{50}'s less than 100 micromolar (WO '425 at internal page 187 at lines 21 and internal page 188 at lines 14-15).

36. Therefore, the POSITA would be taught by both WO '425 and WO '121 to continue to experiment with methyl and hydroxy at the 2' position.

Matsuda *et al* (Published: 1987)

37. The publication by Akira Matsuda *et al* titled "*Radical Deoxygenation of Ter-Alcohols in 2'-branched-chian-sugar pyrimidine nucleosides: synthesis and antileukemic activity of 2'*-deoxy-2'*(S)-methylcytidine*" ("Matsuda *et al*") discloses the synthesis of 2'-deoxy-2'(S)-methylcytidine (see internal page 3967, abstract). It also discloses different substitutions including substitutions at the 2' position of the nucleoside. One such substitution includes methyl(up) and hydroxy (down) substitution. Such substitution is disclosed in Compound 15 (as disclosed on internal page 3968) is reproduced below:



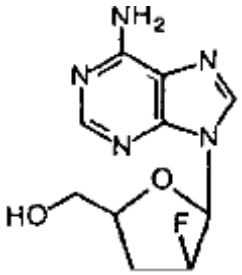
15

38. In fact, Matsuda *et al* **reported an IC_{50} value of 15µg/ml** of the above compound 15**.** (See Matsuda at internal page 3970)
39. Therefore a POSITA working on developing treatment for HCV would be taught by Matsuda about the anti-HCV activity of a compound on substitution of hydroxyl and methyl substitution at the 2'-position of a nucleoside.

Fluorine and hydroxy groups are isosteres

Park *et al* (Published: 1994)

40. The publication by B Kevin Park, Neil R Kitteringham titled, '*Effects of Fluorine Substitution on Drug Metabolism:Pharmacological and Toxicological Implications*' Drug Metabolism Reviews, 26(3), 605-643 (1994) ("Park *et al* ") discusses that success of nucelosides and nucleotides substituted with fluorine, and discloses nucleosides with fluoro substitution, particularly "*A 2'-fluoroarabinosyl substitution in ddAdo (2'F-dd-ara-A), has been found to render the molecule (32) acid stable without loss of antiretroviral activity"* (see internal page 624, lines 3-6). The structure of **compound 32** identified above is reproduced below:



41. Park *et al* also disclose that, "***In addition, fluorine can mimic a hydroxyl group either through dipole-dipole interaction or through an acceptor role in a hydrogen bond.*** *It has been demonstrated that fluorine is capable of interacting significantly with proton donors in enzymatic sites.*" (see internal page 630 at lines 3-11). Park *et al* point out that, "*The introduction of fluorine into a molecule can alter both the rate and route of drug metabolism, in a manner dependent on the sites of metabolic attack in the nonflurinated molecule. Fluorine substitution can also influence the disposition of a drug, and fluorinated drugs have a distinct advantage that their in vivo tissue pharmacokinetics can be monitored noninvasively by* ^{19}F *magnetic resonance spectroscopy. Substitution of fluorine for hydrogen at the site of oxidative attack can block metabolism or can deflect metabolism along an alternative route…In terms of drug design, fluorine substitution can be used to alter the rate of drug metabolism and thereby produce a drug with a longer duration of action, and such an approach has already been used successfully for several classes of drugs. Alternatively, introduction of fluorine could, in theory, improve the therapeutic ratio of drugs which cause toxicity in man by the formation of chemically reactive metabolites. This could be achieved by fluorine substitution at the appropriate site of the molecule, with an alteration in the balance between activation and detoxication*

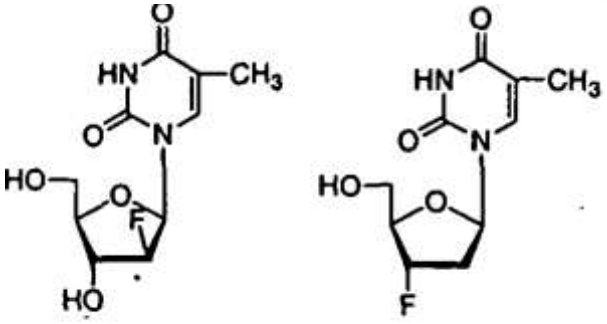
processes; provided, of course, that fluorine is introduced into the molecule in such a way that does not interfere with the interaction between the drug and its pharmacological site of action." Emphasis supplied (see internal page 637, lines 8-14 and lines 26-37).

42. Therefore, a person skilled in the art reading Park *et al* would not only be motivated to use fluorine instead of hydroxyl compound but also be taught that substitution of fluorine could be used to reduce toxicity and produce a drug with longer action.

Fluorine was used for enhancing metabolism and fluorine could be introduced in the nucleoside through *inter alia* Diethylaminosulfur Trifluoride (DAST) process

Pankiewicz (Published: 2000)

43. The publication by Krzysztof W. Pankiewicz, titled "*Fluorinated Nucleosides"* Carbohydrate Research 327 (2000) 87-105 ("Panckeiwicz") noted that " *Introduction of fluorine atom(s) into components of nucleic acids in general and nucleosides in particular frequently leads to dramatic change in their biological activity. For example, replacement of the 2'-β-hydrogen atom (arabino configuration) or the 3'-hydroxyl group of natural thymidine by fluorine afforded new nucleosides with potent antiviral properties FMAU[5] and FLT [6], respectively.*" (see internal page 88, LHS column, lines 32-39). The nucleosides identified as FMAU and FLT are reproduced below (see internal page 88):

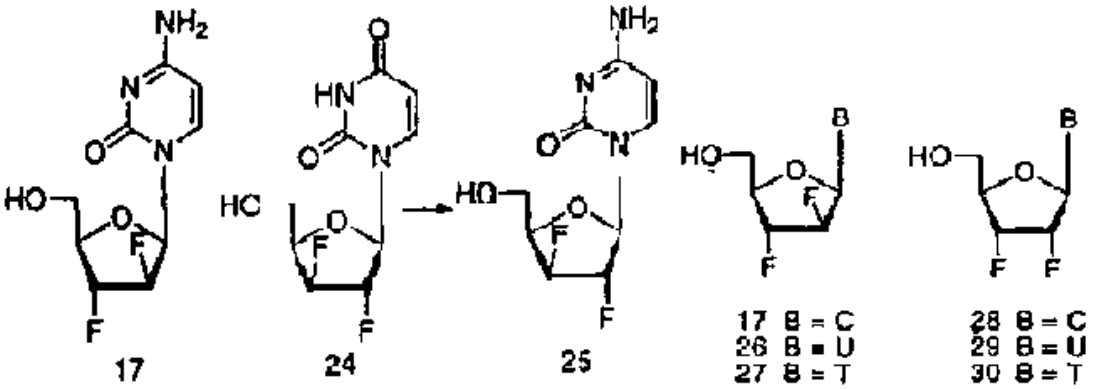


44. In fact, Pankiewicz motivates a person skilled in the art to substitute the hydroxyl group at the 2' position with fluorine when it states that "*since hydrogen or a hydroxyl group at C-2' distinguishes nucleosides as components of deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), it was interesting to investigate the biological properties of nucleosides containing fluorine that could mimic both H or OH to some extent.*" (see internal page 89, LHS column at lines 1-6). It is pertinent to point out Pankeiwicz talks about multiple studies conducted in this regard stating, "*The easy access to the 2-deoxy-2-fluoroarabino sugar resulted in an avalanche of studies on the synthesis of 2'-edoxy-2'fluorinated nucleosides."* (see internal page 90, RHS column, last paragraph).

45. Pankiewicz also discloses the use of DAST for introduction of fluorine in the nucleoside ring in various experiments (See scheme 5 at internal page 91 bottom, scheme 11 at internal page 95).

46. Pankiewicz (on internal page 91) also discusses positions where if nucleoside is substituted with fluorine, the compound would show no activity. It stated that, "*Marquez et al examined the relationship between preferred ring-puckering of fluorine-substituted dideoxynucleosides in solution and their anti-HCV activity. He concluded that, for various aglycone moieties, a fluorine atom at positions 3`-'down' or 2`-'up' correlates with anti-HCV activity,*

whereas, nucleosides with fluorine atoms in the same positions but in inverted configuration are inactive.. Interestingly, he prepared difluorodideoxy xylo-uridine (24) and xylo-cytidine(25) (scheme 5)and found them inactive. With the exception of ara-C analog 17, earlier synthesized difluoro derivatives of ara-U, ara-T(26, 27), as well as the compounds containing two fluorine atoms in the ribo configuration (28-30) did not show any activity." (see internal page 91, RHS column at lines 1-8). Compounds 17, 24-30 are reproduced below for easy reference:



47. Therefore, a POSITA working on developing HCV treatment, on reading Pankiewicz, would be motivated to examine whether a nucleoside would show anti-HCV activity when the substitution of fluorine atoms is varied at the 2' or 3' position of the nucleoside.

Middleton (Published:1975)

48. The publication by William J. Middleton titled, " *New Flourinating Reagents, Dialkylaminosulfur Fluorides*" ("Middleton") points out that "*Dialkylaminosulfur trifluorides and bis(dialkylamino)sulphur difluorides are easy to handle fluorinating reagents useful for replacing*

hydroxyl and carbonyl oxygen with fluorine under very mild conditions…these fluorides were particularly useful in fluorinating sensitive alcohols and aldehydes. For example, reaction of diethylaminosulfur trifluoride (DAST) with isobutyl alcohol gave isobutyl fluoride as the principal product…" (see internal page 574, abstract)

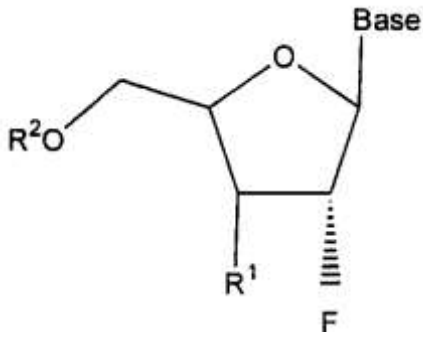
49. *Middleton* particularly points out that the "*reaction of DAST and other dialkylaminosulfur trifluorides with alcohols to replace the hydroxyl group with fluorine appears to be broadly general reaction with distinct advantage over reagents used for this purpose, including SF_4, SeF_4, pyrimidine, α-fluorinated amines, and HF and HF-amine reagents. Primary, secondary and tertiary alcohols all react, with high yields of the unarranged fluorine usually resulting.These reactions can be conducted under very mild conditions so that other groups including ester groups and other halogens, can also be present."* (see internal page 575, RHS column, lines 5-13 and internal page 576, LHS column , para 1).Some examples of fluorine replacing hydroxyl group on treatment with DAST, as disclosed in *Middleton* (internal page 576, LHS column)

50. Hence, a POSITA trying to substitute fluorine with hydroxyl would have access to known processes such as DAST for fluorination.

WO/1999/43691 (Published: September 2, 1999)

51. WO/1999/43691 titled "*2'-Fluronucleosides*" ("WO '691"), discloses 2'-fluoronucleosides "*which are useful in the treatment of Hepatitis B infection, hepatitis C infection, HIV and abnormal cellular proliferation, including tumors and cancer*" (see abstract of WO '691 Application). WO '691 Application discloses a nucleoside with fluorine in down

position at the 2'-position. The structure of the 2'-fluronucleoside as disclosed is reproduced below (See WO '691 on internal page 9):



Where base is a purine or **pyrimidine** base;

R^1 is **OH, H**, OR^3, N_3, CN, Halogen, including F, or CF_3, lower alkyl , amino, loweralkylamino, di(lower)alkylamino, or alkoxy;

R^2 is H, phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; acyl, or other pharmaceutically acceptable leaving group which when administered *in vivo*, is capable of providing a compound wherein R^2 is H or phosphate; sulfonate ester including alkyl or arylalkyl sufonyl including methanesulfonyl, benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given above, a lipid, including phospholipid, an amino acid, peptide, or cholesterol; and

R^3 is acyl, alkyl, phosphate, or other pharmaceutically acceptable leaving group when administered *in vivo*, is capable of being cleaved to the parent compound.

52. WO '691 identifies that "*these 2'-fluronucleosides can be either in the β-L or β-D configuration.*" (internal page 11, WO '691 Application). Pertinently, it states that, "*Fluorine is usually introduced into these molecules through nucleophillic attack on an anhydro-nucleoside or through replacement and inversion of a sterochemically fixed hydroxyl*

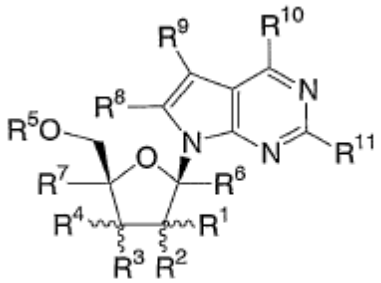
group with diethylaminosulfur trifluoride ***(DAST)****. One advantage of the present methodology is that no hydroxyl group is needed for fluorine introduction. Thus, the process is not limited to natural nucleosides or sugars as starting materials, and provides an easy access to the unnatural enantiomers of the 2'-fluoro nucleosides"* (internal page 33 at lines 7-14 and internal page 29, WO '691)

53. Therefore, a POSITA trying to introduce fluorine in the nucleoside ring could do so with or without the presence of a hydroxyl group on the nucleoside ring.

iii) Particular substitution of methyl and fluorine at 2' position of the identified nucleoside was known

WO 02/057287 (Published: July 25, 2002)

54. WIPO publication No. WO 02/057287 titled '*Nucleoside derivatives as inhibitors of RNA- dependent RNA viral polymerase*' ("WO '287") discloses "*…nucleoside compounds and certain derivatives thereof… for the inhibition of HCV replication and/or the treatment of HCV infection."* (internal page 4 at placitum 11-15). It also discloses 2'-methyl-up 2'-fluorine-down nucleoside analogues in Formula I as below (*See* internal page 5-6):



(I)

or a pharmaceutically acceptable salt thereof:

wherein R^1 is C_{2-4} alkenyl, C_{2-4} alkynyl, or **C_{1-4} alkyl**, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C_{1-4} alkoxy, C_{1-4} alkylthio, or one to three fluorine atoms;

R^2 is hydrogen, **fluorine**, hydroxyl, mercapto, C_{1-4} alkoxy, or C_{1-4} alkyl; or R^1 and R^2 together with the carbon atom to which they are attached to from a 3-6- membered saturated monocyclic ring system optionally containing a heteroatom selected from O, S, and NC_{0-4} alkyl;

R^3 and R^4 are each independently selected from the group consisting of **hydrogen**, cyano, azino, halogen, **hydroxy**, mercapto, amino, C_{1-4} alkoxy, C_{2-4} alkenyl, C_{2-4} alkynyl, and C_{1-4} alkyl, wherein alkyl is unsubstituted or substituted with hydroxy, amino, C_{1-4} alkoxy, C_{1-4} alkylthio, or one to three fluorine atoms;

R^5 is **hydrogen**, C_{1-10} alkylcarbonyl, $P_3O_9H_4$, $P_2O_6H_3$, or $P(O)R_{13}R_{14}$;

R^6 and R^7 are each independently **hydrogen**, methyl, hydroxymethyl, or fluoromethyl;

R^8 is hydrogen, C_{1-4} alkyl, C_{2-4} alkynyl, halogen, cyano, carboxy, C_{1-4} alkyloxycarbonyl, azido, amino, C_{1-6} alkylsulfonyl, $(C_{1-4}$ alkyl$)_{0-2}$ aminomethyl, or C_{4-6} cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C_{1-4} alkyl, and C_{1-4} alkoxy;

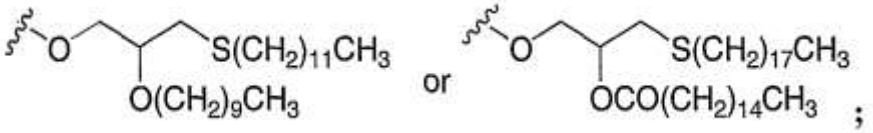
R^9 is hydrogen, cyano, nitro, C_{1-3} alkyl, $NHCONH_2$, $CONR^{12}R^{12}$, $CSNR^{12}R^{12}$, $COOR^{12}$, $C(=NH)NH_2$, hydroxyl, C_{1-3} alkoxy, amino, C_{1-4} alkyl)amino, di(C_{1-4} alkyl)amino, halogen, (1,3-oxazol-2-yl), (1,3-thiazol-2-yl), or (imidazol-2-yl); wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, amino, hydroxyl, carboxy, and C_{1-3} alkoxy;

R^{10} and R^{11} are each independently hydrogen, hydroxy, halogen, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6}

cycloalkylamino, di(C_{3-6}cycloalkyl)amino, or C_{4-6} cycloheteroalkyl, unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, amino, C_{1-4} alkyl, and C_{1-4} alkoxy;

Each R^{12} is independently hydrogen or C_{1-6} alkyl; and

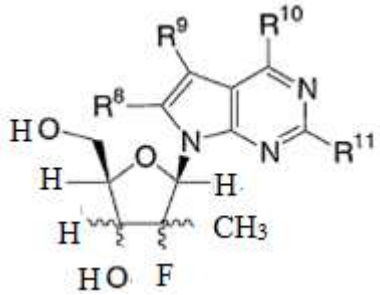
R^{13} and R^{14} are each independently hydroxyl, $OCH_2CH_2SC(=O)C_{1-4}$alkyl, $OCH_2O(C=O)OC_{1-4}$alkyl, $NHCHMeCO_2Me$, $OCH(C_{1-4}$alkyl$)O(C=O)C_{1-4}$ alkyl,



;

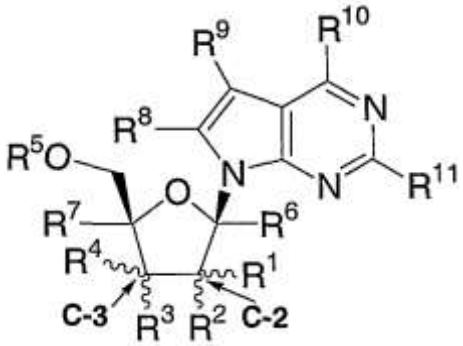
with the proviso that when R^1 is β-methyl and R^4 is hydrogen or R^4 is β-methyl and R^1 is hydrogen, R^2 and R^3 are α-hydroxy, R^{10} is amino, and R^5, R^6, R^7, R^8, and R^{11} are hydrogen, then R^9 is not cyano or $CONH_2$.

55. When the substitutions (as emphasized above) are made on Formula I, the following compound is obtained:



56. In fact, the WO '287 Application discloses that, "*The stereochemistry of the substituents at C-2 and C-3 positions* (these carbon atoms are identified in the structure reproduced below) *of the furanose ring of the compounds of the present invention of structural formula I is denoted by squiggly lines which signifies that substituent R^1, R^2, R^3, R^4 can have either α (substituents "down") or β (substituents "up")*

configuration independently of one another. Notation of stereochemistry by a bold line as at C-1 and C-4 of the furanose ring signifies that the substituent has the β-configuration (substituent "up")." (see internal page 22 at placitum 8-14). The C-2 and C-3 carbons have been identified in the structure below:



57. Also, out of the 38 examples identified in WO '287, at least 27 of them have CH_3 substitution at the 2'-position of the nucleoside with β-D configuration (see internal pages 22 through 68).

58. Therefore, a person skilled in the art on reading WO '287 would be taught to attempt different disclosed substituents along with CH_3 at the R^2 position of the nucleoside with β-D configuration.

59. In summary, on reading on the prior art documents discussed above- A POSITA on reading WO '425 and WO '121 would be taught that in a nucleoside being developed for treatment of HCV, the substitution of methyl and hydroxyl group at the 2' position of nucleoside may be explored on that such compounds may have IC_{50}'s less than 100 micromolar. On reading Matsuda *et al* the POSITA would be taught that a substitution of methyl and hydroxyl

group at the 2' position in particular shows an activity of IC_{50} value of 15µg. On reading Park *et al* POSITA would be taught that introduction of Fluorine in place of hydroxyl may improve the therapeutic ratio of drugs which cause toxicity by the formation of chemically reactive metabolites, and may also increase the duration of action of a drug. On reading, Pankiewicz and WO '691, a POSITA would be further motivated to substitute fluorine at the 2' position of the nucleoside as Pankiewicz discloses that a fluorine atom at positions 3`-'down' or 2`-'up' correlates with anti-HCV activity, and fluorine atom could be substituted by a simple DAST process. WO '691 would also motivate a POSITA to examine both- β-L or β-D configuration of the 2'-fluronucleosides. Further, Middleton would teach that a fluorine atom may be substituted even without the DAST process. Reading of WO '287 would further motivate the POSITA to make such substitutions at the 2'-position as it discloses at least 27 examples with CH_3 substitution at the 2'-position of the nucleoside with β-D configuration. On reading these prior art documents together a POSITA working on developing HCV treatment would have a reasonable expectation of success in arriving at the compound as claimed in the opposed application.

60. Therefore, I would opine that the claimed invention is not inventive.

Anand Grover

Senior Advocate

Former UN Special Rapporteur on the right of everyone to the enjoyment of the highest attainable standard of physical and mental health

Dated this 30th day of August, 2018

IV. DO PEDIDO

Como acima exposto, as duas reivindicações que compõem o quadro reivindicatório atual descumprem todos os requisitos e condições estipulados pela LPI para a concessão de patentes de invenção. Dessa forma as organizações interessadas requerem:

a) Que o presente subsídio seja conhecido e que passe a compor o escopo processual do pedido de patente em análise, vez que preenche os critérios de admissibilidade (tempestividade e legitimidade) estabelecidos em Lei;

b) Que os documentos apresentados na presente petição, assim como nas três petições anteriores, **sejam expressamente considerados por este Instituto** e que eventual afastamento de sua pertinência ao caso concreto seja realizado **mediante motivação expressa e fundamentada**, conforme disposto no artigo 3º, III e artigo 50 ambos da Lei nº 9.784/1999, que regula os processos administrativos no âmbito da administração pública federal;

c) Que seja **indeferido** o pedido de patente de invenção **PI0410846-9** em sua totalidade, uma vez que **todas as reivindicações formuladas deixam de cumprir os requisitos de patenteabilidade** estabelecidos na LPI.

Nestes termos,

Pede Deferimento.

Rio de Janeiro, 03 de setembro de 2018.

Carolinne Thays Scopel
CRF/RJ 20.318

Marcela Fogaça Vieira
OAB/SP 252.930

LISTA DE DOCUMENTOS ANEXOS:

ANEXO 1: Furman, P. A.; Otto, M. J.; Sofia, M. J. Discovery and development of PSI-6130/RG7128. Antiviral Drugs: From Basic Discovery through Clinical Trials, 2011.

ANEXO 2: Vere Hodge, R. A. Meeting report: 28th International Conference on Antiviral Research in Rome, Italy. Antiviral Research 123, p. 172–187, 2015.

ANEXO 3: Meijer, A. Development of a novel promoter system for thioglycoside activation and its application in the synthesis of a GD3 bis-lactam. Lund University, 2003.

ANEXO 4: WO 2001/90121. Publicado em: 29 de novembro de 2001.

ANEXO 5: WO 2002/057425. Publicado em: 25 de julho de 2002.

ANEXO 6: Matsuda et al. Radical Deoxygenation of Ter-Alcohols in 2'-branched-chian-sugar pyrimidine nucleosides: synthesis and antileukemic activity of 2'-deoxy-2'(S)-methylcytidine, 1987.

ANEXO 7: Park, B. K.; Kitteringham, N. R. Effects of Fluorine Substitution on Drug Metabolism: Pharmacological and Toxicological Implications. Drug Metabolism Reviews, 26(3), 605-643, 1994.

ANEXO 8: Pankiewicz, K. W. Fluorinated Nucleosides. Carbohydrate Research 327, 87-105, 2000.

ANEXO 9: Middleton, W. J. New Flourinating Reagents, Dialkylaminosulfur Fluorides, 1975.

ANEXO 10: WO 1999/43691. Publicado em: 02 de setembro de 1999.

ANEXO 11: WO 2002/057287. Publicado em: 25 de julho de 2002.

ANEXO 12: Opinião técnica do especialista Dr. Anand Grover.

ANEXO 13: Perfil do Dr. Anand Grover.