专 利 权 无 效 宣 告 请 求 书

请按照“注意事项”正确填写本表各栏　　LWI16US0497

此框内容由专利复审委员会填写
①案件编号

②专利	专利号　200480019148.4　授权公告日　2009 年 06 月 24 日		
	发明创造名称　修饰的氟化核苷类似物		
	专利权人　吉利德制药有限责任公司		
③无效宣告请求人	姓名或名称	医药、使用权和知识倡议(I-MAK)公司	电话
	居民身份证件号或组织机构代码地址		
	电子邮箱		
	国籍或注册国家(地区)　美国	经常居所地或营业所所在地	
	邮政编码　19958-9776	详细地址　苏塞克斯县 19958-9776 特拉华州刘易斯滨海公路 16192	
④收件人	姓　名	电话	电子邮箱
	邮政编码	详细地址	

⑤专利代理机构	名　称　北京三友知识产权代理有限公司				机构代码　11127
	代理人(1)	姓　名	庞东成	代理人(2) 姓　名	武胍
		执业证号	1112708310.6	执业证号	1112714962.9
		电　话	010-88091921	电　话	010-88091921

⑥

根据专利法第 45 条及专利法实施细则第 65 条规定，对上述专利权提出无效宣告请求。

⑦ 无效宣告请求的理由、范围及所依据的证据

理　由	范围	依据的证据
专利法第 22 条第 2 款	权利要求 1	证据 1 或证据 3
专利法第 22 条第 3 款	权利要求 1	证据 1 证据 4+公知常识 证据 4+证据 6，证据 4+证据 6 和 7， 证据 4+证据 8，证据 4+证据 7 和 8， 以上证据组合+公知常识
专利法第 22 条第 3 款	权利要求 2-12、权利要求 15-16	与评价权利要求 1 的证据组合相同
专利法第 22 条第 2 款	权利要求 5-7、权利要求 11-12、 权利要求 15-16	与评价权利要求 1 的证据组合相同
专利法第 26 条第 4 款(说明书支持)	权利要求 1-5、7-11、13-16	
专利法第 26 条第 3 款	权利要求 1-5、7-11、13-16	

专 利 权 无 效 宣 告 请 求 书

⑧ 结合证据对无效宣告请求理由的具体陈述意见：

（详见附页）

⑨附件清单

文件名称	份数及页数
☒附件 1　证据 1：WO2004002999	2 份，每份 201 页
☒附件 2　证据 2：US 60/474,368；及其部分中文译文	2 份，每份 46 页
☒附件 3　证据 3：CN1761677A	2 份，每份 156 页
☒附件 4　证据 4：WO0190121A2，及其中文译文	2 份，每份 579 页
☒附件 5　证据 5：《基础药物设计学》(1995)，陈芬儿编著	2 份，每份 19 页
☒附件 6　证据 6：McAtee 等(1998)，及其部分中文译文	2 份，每份 8 页
☒附件 7　证据 7：Carroll 等(2003) ，及其部分中文译文	2 份，每份 8 页
☒附件 8　证据 8：CN1332747A	2 份，每份 97 页
☒附件 9　无效请求委托书原件	1 份，每份 1 页
☒附件 10 无效请求人的公司工商登记文件的复印件及其中译文	1 份，每份 6 页
☒附件 11 无效请求缴费收据	1 份，每份 1 页

⑩ 无效宣告请求人或专利代理机构签字或者盖章	Ω 专利复审委员会处理意见
BEIJING SANYOU INTELLECTUAL PROPERTY AGENCY LTD. 北京三友知识产权代理有限公司 代理专用章 2017 年 04 月 19 日	年　月　日

101001
2010.4

尊敬的复审委员会：

针对 ZL200480019148.4 号专利(下文称之为争议专利)，请求人 I-MAK 依法提出以下无效请求。

一、争议专利基本信息

专利号：200480019148.4；

授权时的专利权人：法莫赛特股份有限公司(美国新泽西)

当前专利权人：吉利德制药有限责任公司

申请日：2004 年 4 月 21 日；

优先权日：2003 年 5 月 30 日；

国际申请号(公开号)：PCT/US2004/012472 (WO 2005003147)

国际申请的申请人：法莫赛特有限公司(巴巴多斯)

中国授权公告日：2009 年 6 月 24 日；

发明名称：修饰的氟化核苷类似物

二、证据

证据 1：WO2004002999 (证据 3 可作为证据 1 的中文译文)；

证据 2：US 60/474,368；以及部分中文译文；

证据 3：CN1761677A；

证据 4：WO0190121A2 (其中文同族 CN1443191A 可作为其中文译文)

证据 5：《基础药物设计学》，1995 年，陈芬儿编著

证据 6：McAtee 等，A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2'-Fluoronucleosides，J. Org. Chem, 1998, 63, 2161-2167，及其部分中文译文；

证据 7：Carroll 等，Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs, THE JOURNAL OF BIOLOGICAL CHEMISTRY, Vol. 278, No. 14, Issue of April 4, pp. 11979–11984, 2003，及其部分中文译文；

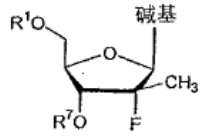
证据 8：CN1332747A。

【注】证据 2 获自 WIPO 官方网站，网址为：

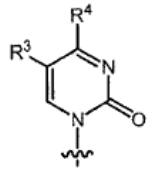
https://patentscope.wipo.int/search/docservicepdf_pct/id00000001713395/PDOC/WO2005003147.pdf

三、争议专利的权利要求

1. 通式如下的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或 β-L-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷，或其药学上可接受的盐：



其中，碱基是以下结构式所示的嘧啶碱基：



R^1 和 R^7 独立地是 H，C_1-C_{10} 烷基，C_1-C_{10} 烷基磺酰基或芳基 C_1-C_{10} 烷基磺酰基，所述芳基选自苯基、联苯基或萘基，或者，R^1O-和 R^7O-独立地是单磷酸酯基，二磷酸酯基，三磷酸酯基或 H-膦酸酯基；

R^3 是 H，R^4 是 OH 或 NH_2。

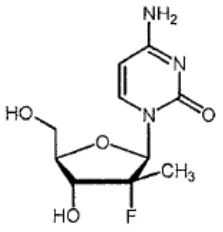
2. 如权利要求 1 所述的的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或 β-L-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷，或其药学上可接受的盐，其中，R^7 是 H，R^1O-是单磷酸酯基，二磷酸酯基或三磷酸酯基。

3. 如权利要求 1 所述的的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷，或其药学上可接受的盐，其中，R^7 是 H，R^1O-是二磷酸酯基或三磷酸酯基。

4. 如权利要求 1 所述的的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或 β-L-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷，或其药学上可接受的盐，其中，R^7 是 H，R^1O-是三磷酸酯基。

5. 如权利要求 1 所述的的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或 β-L-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷，或其药学上可接受的盐，其中，R^1 和 R^7 都是 H。

6. 通式如下的 β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或其药学上可接受的盐：



。

7. 一种药物组合物，包含权利要求 1 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

8. 一种药物组合物，包含权利要求 2 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

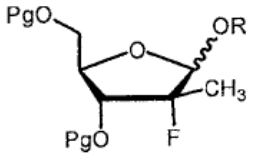
9. 一种药物组合物，包含权利要求 3 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

10. 一种药物组合物，包含权利要求 4 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

11. 一种药物组合物，包含权利要求 5 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

12. 一种药物组合物，包含权利要求 6 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

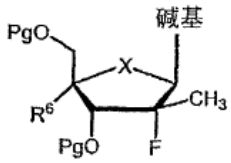
13. 一种合成权利要求 1 所述核苷的方法，所述方法包括用以下结构的化合物糖基化嘧啶碱：



1-4

其中，R 是 C_{1-10} 烷基、酰基、苯甲酰基或甲磺酰基；Pg 选自：C(O)-C_{1-10} 烷基、C(O)Ph、C(O)芳基、CH_3、CH_2-C_{1-10} 烷基、CH_2-C_{2-6} 烯基、CH_2Ph、CH_2-芳基、CH_2O-C_{1-10} 烷基、CH_2O-芳基、SO_2-C_{1-10} 烷基、SO_2-芳基、叔丁基二甲基甲硅烷基、叔丁基二苯基甲硅烷基，或两个 Pg 可连接在一起形成 1,3-(1,1,3,3-四异丙基二亚硅氧烷基)，所述所述芳基选自苯基、联苯基或萘基。

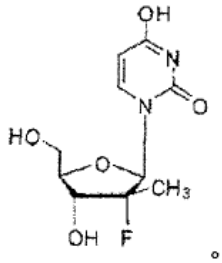
14. 一种合成权利要求 1 所述核苷的方法，所述方法包括如下中间体结构中 3'-OPg 或 5'-OPg 的选择性脱保护：



2-5

其中，X 是 O；Pg 独立地是选自下列的任何药学上可接受的保护基：C(O)-C_{1-10}烷基、C(O)Ph、C(O)芳基、CH_3、CH_2-C_{1-10}烷基、CH_2-C_{2-6}烯基、CH_2Ph、CH_2-芳基、CH_2O-C_{1-10}烷基、CH_2O-芳基、SO_2-C_{1-10}烷基、SO_2-芳基、叔丁基二甲基甲硅烷基、叔丁基二苯基甲硅烷基，或两个 Pg 可连接在一起形成1,3-(1,1,3,3-四异丙基二亚硅氧烷基)，所述所述芳基选自苯基、联苯基或萘基。

15. 通式如下的β-D-(2'*R*)-2'-脱氧-2'-氟-2'-*C*-甲基核苷或其药学上可接受的盐：



。

16. 一种药物组合物，包含权利要求 15 所述的核苷或其药学上可接受的盐和药学上可接受的载体。

四、无效的事实与理由

请求人的事实与理由如下表所示：

权利要求	法律依据	证据组合
1	专利法第 22 条第 2 款	证据 1 或证据 3
1	专利法第 22 条第 3 款	证据 1 证据 4+公知常识 证据 4+证据 6，证据 4+证据 6 和 7，证据 4+证据 8，证据 4+证据 7 和 8，以上证据组合+公知常识
2	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
3	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
4	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
5	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
5	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
6	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
6	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
7	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
7	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
8	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同

9	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
10	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
11	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
11	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
12	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
12	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
15	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
15	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
16	专利法第 22 条第 2 款	与评价权利要求 1 的证据组合相同
16	专利法第 22 条第 3 款	与评价权利要求 1 的证据组合相同
1-5、7-11、13-16	专利法第26条第4款支持	
1-5、7-11、13-16	专利法第 26 条第 3 款	

五、具体事实和理由

5.1 争议专利的权利要求 1-12、15-16 相对于证据 1 (WO2004002999)不具备新颖性或创造性

5.1.1 证据 1 作为对比文件的有效性

证据 3 (CN1761677A)是证据 1 在中国国家阶段的申请，证据 3 可以作为证据 1 的中文译文。

证据 1 的公开日为 2004 年 1 月 8 日，早于争议专利的申请日 2004 年 4 月 21 日，晚于争议专利的优先权日 2003 年 5 月 30 日。但是，请求人认为争议专利并不能享受该优先权日。

1)专利法第 29 条规定：“申请人自发明或者实用新型在外国第一次提出专利申请之日起十二个月内，或者自外观设计在外国第一次提出专利申请之日起六个月内，又在中国就相同主题提出专利申请的，依照该外国同中国签订的协议或者共同参加的国际条约，或者依照相互承认优先权的原则，可以享有优先权”。即，专利法明确了要求优先权的在后申请与在先申请的申请人必须是同一人。

但是，争议专利在递交国际申请时(2004 年 4 月 21 日)，其申请人是“法莫赛特有限公司(巴巴多斯)”(**Pharmasset, Ltd (Barbados)**)，而其要求优先权的在先申请 **US 60/474,368 (证据 2)**的申请人是 **Jeremy Clark** 和 **Lieven Stuyer**，而且截止此日，并没有证据表明 Jeremy Clark 和 Lieven Stuyer 在 2004 年 5 月 30 日前将在先申请的权益转让给了法莫赛特有限公司(巴巴多斯)。即，争议专利的申请

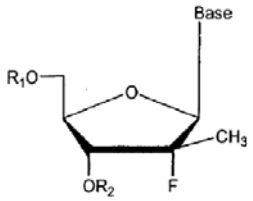
人在递交专利申请时与在先申请的申请人完全不同，按照专利法 29 条的规定，争议专利的申请人法莫赛特有限公司(巴巴多斯)在申请日时无权要求在先申请的优先权，其优先权请求应视为无效。

因此，请求人认为争议专利的优先权不能成立，在其申请日 2014 年 4 月 21 日之前公开的技术均构成其现有技术，证据 1 可以用作争议专利的对比文件。

2)争议专利的优先权文本证据 2 (US 60/474,368)没有公开争议专利权利要求 1-5、7-11、13-16 的技术方案，因此，争议专利的权利要求 1-5、7-11、13-16 及对应技术方案不能享受优先权。

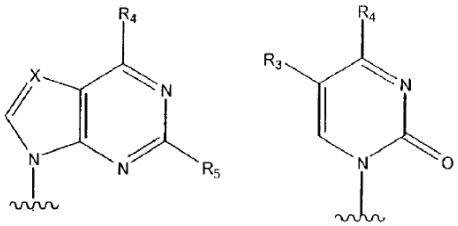
证据 2 在第 7-8 页公开了以下技术方案：

“在一个实施方式中，所述抗病毒有效的核苷是通式(I)的 β-D 或 β-L 核苷或其药学上可接受的盐或前药：



(I)

其中，Base 可以是



其中：

(a) X=N 或 CH。

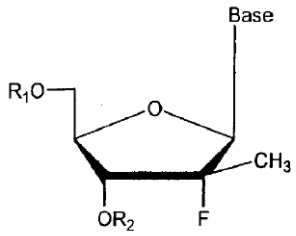
(b) R1 和 R2 独立地为：H；磷酸酯(包括单磷酸酯、二磷酸酯、三磷酸酯或稳定的磷酸酯前药)；H-膦酸酯(包括稳定的 H-膦酸酯)；酰基[包括苯基(任选地经取代的)、低级酰基]；烷基(包括低级烷基、O-取代羧基烷基氨基或其肽衍生物)；磺酸酯，包括烷基或芳烷基磺酰基，包括甲磺酰基和苄基，其中苯基被本文给出的芳基的定义中所描述的一种或多种取代基任选地取代；脂质，包括磷脂；氨基酸；碳水化合物；肽，胆固醇；或其它药学上可接受的离去基团，体内给药时，所述离去基团能够提供一种化合物，其中 R1 或 R2 独立地是 H 或膦酸酯(来

自 WO01/90121)。

(c) R3、R4 和 R5 独立地是 H、卤素(F、Cl、Br、I)、OH、OR'、SH、SR'、NH_2、NHR'、NR'_2、C_1-C_6 低级烷基、C_1-C_6 卤代(F、Cl、Br、I)低级烷基如 CF_3 和 CH_2CH_2F、C_2-C_6 低级烯基如 $CH=CH_2$、C_2-C_6 卤代(F、Cl、Br、I)低级烯基如 CH=CHCl、CH=CHBr 和 CH=CHI、C_2-C_6 低级炔基如 C≡CH、C_2-C_6 卤代(F、Cl、Br、I)低级炔基、C_1-C_6 低级烷氧基如 CH_2OH 和 CH_2CH_2OH、CO_2H、CO_2R'、$CONH_2$、CONHR'、$CONR'_2$、$CH=CHCO_2H$、$CH=CHCO_2R'$。"

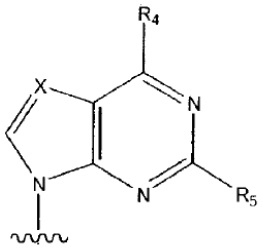
另外，证据 2 在第 15-16 页公开了以下技术方案：

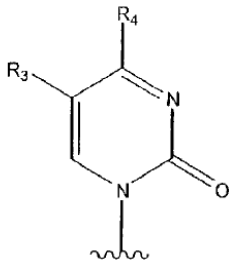
"在一个实施方式中，所述抗病毒或抗增殖有效的核苷是通式(I)的β-D 或 β-L 核苷或其药学上可接受的盐或前药：



(I)

其中，Base 可以是





其中：

a. X=N 或 CH。

b. R1 和 R2 独立地为：H；磷酸酯(包括单磷酸酯、二磷酸酯、三磷酸酯或稳定的磷酸酯前药)；H-膦酸酯(包括稳定的 H-膦酸酯)；酰基[包括苯基(任选地经取代的)、低级酰基]；烷基(包括低级烷基、O-取代羧基烷基氨基或其肽衍生物)；磺酸酯，包括烷基或芳烷基磺酰基，包括甲磺酰基和苄基，其中苯基被本文给出的芳基的定义中所描述的一种或多种取代基任选地取代；脂质，包括磷脂；氨基酸；碳水化合物；

肽，胆固醇；或其它药学上可接受的离去基团，体内给药时，所述离去基团能够提供一种化合物，其中 R1 或 R2 独立地是 H 或膦酸酯(来自 WO01/90121)。

c. R3、R4 和 R5 独立地是 H、卤素(F、Cl、Br、I)、OH、OR'、SH、SR'、NH_2、NHR'、NR'$_2$、C_1-C_6 低级烷基、C_1-C_6 卤代(F、Cl、Br、I)低级烷基如 CF_3 和 CH_2CH_2F、C_2-C_6 低级烯基如 $CH=CH_2$、C_2-C_6 卤代(F、Cl、Br、I)低级烯基如 CH=CHCl、CH=CHBr 和 CH=CHI、C_2-C_6 低级炔基如 C≡CH、C_2-C_6 卤代(F、Cl、Br、I)低级炔基、C_1-C_6 低级烷氧基如 CH_2OH 和 CH_2CH_2OH、CO_2H、CO_2R'、$CONH_2$、CONHR'、CONR'$_2$、$CH=CHCO_2H$、$CH=CHCO_2R'$。"

此外，证据 2 在第 21 页公开了低级烷基的定义：

"除非另有具体说明，本文所用的术语"低级烷基"是指 C_1-C_4 饱和直链、支化或适当时为环状的(例如环丙基)烷基"。

在上述两个技术方案以及证据 2 的其余部分，均没有具体公开争议专利权利要求 1-5、7-11、13-16 的技术方案。例如(但不限于此)，证据 2 并未具体公开 R1 和 R2(对应于争议专利的 R^1 和 R^7)取 C_1-C_{10} 烷基、C_1-C_{10} 烷基磺酰基、芳基 C_1-C_{10} 烷基磺酰基的情形。

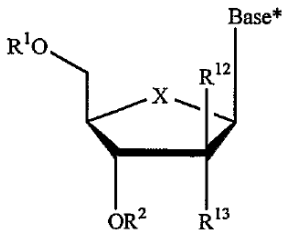
因此，争议专利的权利要求 1-5、7-11、13-16 以及说明书中对应于这些权利要求的技术方案均不能享受优先权。在其申请日 2014 年 4 月 21 日之前公开的技术均构成其现有技术，证据 1 可以用作争议专利的上述技术方案及权利要求的对比文件。

5.1.2 争议专利的权利要求 1、5-7、11、12、15、16 相对于证据 1 (WO2004002999)不具备新颖性

证据 1 公开了一种用于预防和治疗黄病毒感染(包括丙肝病毒 HCV)的核苷类似物(见例如证据 1 第 1 页 10-13 行)，特别而言，证据 1 的第 100 页第 6-29 行(以及权利要求 9-11)公开了以下技术方案：

"在另一个优选实施方案中，提供了式(IX)的化合物或可药用盐或前

药，或它们的立体异构体、互变异构体或多晶型物，也提供了一种用于治疗感染有黄病毒科病毒的宿主的方法，包含使用有效治疗量的式(IX)的化合物：



(IX)

或可药用盐或前药，或它们的立体异构体、互变异构体或多晶型物，其中：

R^1，R^2 和 R^3 独立地是 **H，磷酸根**；直链、支链或环**烷基**；酰基；CO-烷基；CO-芳基；CO-烷氧基烷基；CO-芳氧基烷基；CO-取代的芳基；磺酸酯；苄基，其中苯基任选被一或多个取代基取代；**烷基磺酰基**；芳基磺酰基；**芳烷基磺酰基**；脂质；氨基酸；氨基酸残基；碳水化合物；肽；胆固醇；或一种药学上可接受的离去基团，当施用于体内时，其能提供其中 R^1，R^2 和/或 R^3 独立地是 H 或磷酸根的化合物；

X 是 O，S，SO_2 或 CH_2；

碱基*(Base*)是嘌呤或嘧啶碱基；

R^{12} 是 $C(Y^3)_3$；

Y^3 独立地是 H，F，Cl，Br 或 I；和

R^{13} 是氟。

在一个分实施方案中 **X 是 O，和 Y^3 是 H**。在另一个分实施方案中，当 X 是 O 和 Y^3 是 H 时，**R^1，R^2 和 R^3 也是 H**。”

在上述第一个分实施方案中(称之为分实施方案 I)，X 是 O，R^{12} 是甲基，碱基是嘌呤或嘧啶碱基，R^1 和 R^2 (分别对应于争议专利权利要求 1 的 R^1 和 R^7)可以是 H、磷酸酯、烷基、烷基磺酰基、芳烷基磺酰基。

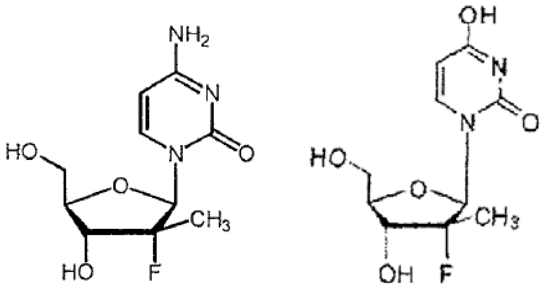
在上述第二个分实施方案中(称之为分实施方案 II)，X 是 O，R^{12} 是甲基，碱基是嘌呤或嘧啶碱基，R^1 和 R^2 均为 H。

此外，证据 1 的定义部分公开了以下内容：第 103 页的 12-14 行公开了“烷

基指通常为1-10个碳原子的饱和直链、支链或环状的伯、仲或叔烃基”；第104页3-4行公开了“芳基指苯基、联苯基或萘基”；第104页15行起公开了“嘌呤或嘧啶碱基包括但不限于胞嘧啶、……尿嘧啶”。

而且，证据1的发明的化合物都是“核苷的2’和3’前药”(见证据1第12页12行)，在天然胞嘧啶核苷(胞苷)和尿嘧啶核苷(尿苷)分子中，胞嘧啶碱基和尿嘧啶碱基均以其1号N原子与戊糖环连接，因此，对于式(IX)中的碱基*而言，证据1的分实施方案II事实上公开了碱基是以1号N原子与戊糖环连接的胞嘧啶碱基和尿嘧啶碱基的特征，即正是争议专利权利要求1中所定义的嘧啶碱基。

可见，证据1的分实施方案II公开了“β-D-(2’R)-2’-脱氧-2’-氟-2’-C-甲基胞苷”和“β-D-(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷”：



它们完全落入争议专利权利要求1的范围内(相当于R^1=R^7=H的情况)。因此权利要求1不具备新颖性。同样地，争议专利的权利要求5、6、15也不具备新颖性。

证据1在第44页(e)-(g)公开了包含证据1的核苷及其药学可接受盐的药物组合物，第117页2-8行公开了包含证据1的各种活性化合物或其前药或盐的药物组合物，第12页6-7行也公开了证据1的目的之一是提供治疗HCV的组合物。

因此，在争议专利的权利要求1、5、6、15不具备新颖性的基础上，其权利要求7、11、12、16也不具备新颖性，因为它们的技术特征已被证据1公开。

5.1.3 权利要求1-12、15-16相对于证据1 (WO2004002999)不具备创造性

争议专利的权利要求1相对于证据1的分实施方案I不具备创造性，因为本领域技术人员在分实施方案I的基础上根据证据1给出的各基团的定义(尤其参见上文的下划线部分)可以常规地选择R^1和R^2(分别对应于争议专利权利要求1的R^1和R^7)为H、C_1-C_{10}烷基、C_1-C_{10}烷基磺酰基、芳基C_1-C_{10}烷基磺酰基、磷酸根(即相当于R^1O或R^2O为单磷酸酯)，其中芳基为苯基、联苯基或萘基。

此外，在核苷的 5’位置选择二磷酸酯基或三磷酸酯基是本领域的常规选择，因为本领域公知参与 DNA/RNA 合成的单元是三磷酸核苷，三磷酸核苷是从非磷酸化的核苷开始经一系列磷酸化反应经由单磷酸核苷、二磷酸核苷而来。因此，在争议专利的权利要求 1 不具备新颖性和创造性的基础上，争议专利的权利要求 2-4 也不具备创造性。

在证据 1 中已经公开了权利要求 5 和 6 的附加技术特征的基础上，权利要求 5 和 6 也不具有创造性。

基于证据 1 对药物组合物的相关公开内容(见 5.1.2)，争议专利的权利要求 7-10 也不具备创造性。

基于证据 1 对药物组合物的相关公开内容(见 5.1.2)，争议专利的权利要求 11-12 也不具备创造性。

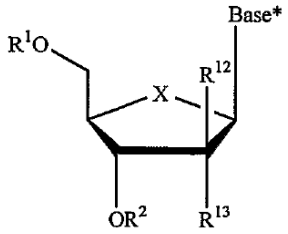
参见 5.1.2，在权利要求 15 和 16 不具有新颖性的基础上，权利要求 15 和 16 也不具有创造性。

5.2 争议专利的权利要求 1、5-7、11、12、15、16 相对于证据 3 (CN1761677A) 不具备新颖性

证据 3 (CN1761677A)是证据 1 在中国国家阶段的申请，其优先权日为 2002 年 6 月 28 日、2003 年 4 月 28 日和 2003 年 5 月 14 日，均早于争议专利的优先权日 2004 年 4 月 21 日(或 2003 年 5 月 30 日，假设优先权成立)，其公开日为 2006 年 4 月 19 日，晚于争议专利的优先权日，因此，证据 3 构成争议专利的抵触申请。

证据 3 在说明书第 74 页(右上角的页码，下同)至 75 页公开了如下技术方案：

> “在另一个优选实施方案中，提供了式(IX)的化合物或可药用盐或前药，或它们的立体异构体、互变异构体或多晶型物，也提供了一种用于治疗感染有黄病毒科病毒的宿主的方法，包含使用有效治疗量的式(IX)的化合物：



(IX)

或可药用盐或前药，或它们的立体异构体、互变异构体或多晶型物，其中：

R^1，R^2 和 R^3 独立地是 H，磷酸根；直链、支链或环烷基；酰基；CO-烷基；CO-芳基；CO-烷氧基烷基；CO-芳氧基烷基；CO-取代的芳基；磺酸酯；苄基，其中苯基任选被一或多个取代基取代；烷基磺酰基；芳基磺酰基；芳烷基磺酰基；脂质；氨基酸；氨基酸残基；碳水化合物；肽；胆固醇；或一种药学上可接受的离去基团，当施用于体内时，其能提供其中 R^1，R^2 和/或 R^3 独立地是 H 或磷酸根的化合物；

X 是 O，S，SO_2 或 CH_2；

碱基*(Base*)是嘌呤或嘧啶碱基；

R^{12} 是 $C(Y^3)_3$；

Y^3 独立地是 H，F，Cl，Br 或 I；和

R^{13} 是氟。

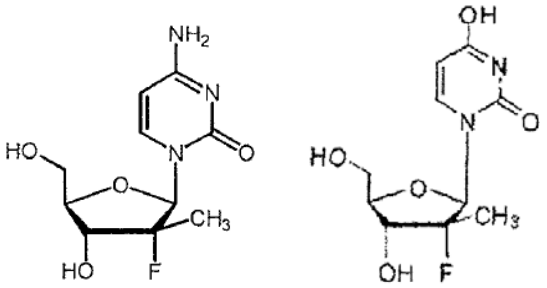
在一个分实施方案中 **X 是 O，和 Y^3 是 H**。在另一个分实施方案中，**当 X 是 O 和 Y^3 是 H 时，R^1，R^2 和 R^3 也是 H**。”

在上述第二个分实施方案中(称之为分实施方案 II)，X 是 O，R^{12} 是甲基，碱基是嘌呤或嘧啶碱基，R^1 和 R^2 均为 H。

此外，证据 3 的定义部分第 77 页倒数第二段公开了“嘌呤或嘧啶碱基包括但不限于胞嘧啶、……尿嘧啶”。

而且，证据 3 的化合物都是“**核苷**的 2’和 3’前药”(见证据 3 说明书第 9 页第 2 行)，在天然胞嘧啶核苷(胞苷)和尿嘧啶核苷(尿苷)分子中，胞嘧啶碱基和尿嘧啶碱基均以其 1 号 N 原子与戊糖环连接，因此，证据 3 的上述分实施方案 II 实质上公开了碱基是以 1 号 N 原子与戊糖环连接的胞嘧啶碱基和尿嘧啶碱基的特征，即争议专利权利要求 1 中所定义的嘧啶碱基。

可见，证据 3 的分实施方案 II 公开了“β-D-(2’R)-2’-脱氧-2’-氟-2’-C-甲基胞苷”和“β-D-(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷”：



它们完全落入争议专利权利要求 1 的范围内(相当于 R^1=R^7=H 的情况)。因此权利要求 1 不具备新颖性。同样地，争议专利的权利要求 5、6、15 也不具备新颖性。

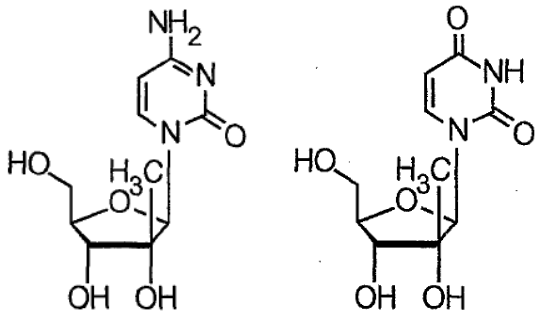
证据 3 在说明书第 32 页(e)-(g)公开了包含证据 3 的各种核苷前药及其药学可接受盐的药物组合物，第 86 页 1-5 行公开了包含证据 3 的各种活性化合物或其前药或盐的药物组合物，第 8 页倒数第二段也公开了证据 3 的目的之一是提供治疗 HCV 的组合物。

因此，基于 5.1.2 中相同的理由，争议专利的权利要求 1、5-7、11、12、15、16 不具备新颖性。

5.3 争议专利的权利要求 1-12 和 15-16 相对于证据 4 或其与其他证据的组合不具备创造性

5.3.1 相对于证据 4 和公知常识

证据 4 (WO 0190121A2)公开一系列抗 HCV 化合物(见第 20 页最后一段)，其中，附图 1 公开了具体化合物 β-D-2’-CH_3-胞苷和 β-D-2’-CH_3-尿苷：



其与争议专利权利要求 1 中的(2’R)-2’-脱氧-2’-氟-2’-C-甲基胞苷/尿苷的区别仅在于，2’-*C* 位置的 α 位为 OH，而争议专利的化合物在相应位置为 F。针对此区

别特征，争议专利的权利要求 1 所要解决的技术问题是：提供一种新的抗 HCV 化合物。

证据 5 (《基础药物设计学》-陈芬儿 1995)中已经记载，F 与 OH 为生物电子等排体(参见证据 5 第 162 页表 8-6 中的“一价等排体”)。本领域技术人员熟知在药物研制中二者可以相互置换，并可能取得类似的技术效果(参见证据 5 第 164 页第 1-2 行)。因此，本领域公知电子等排体的相互替换是药物研发中常用的手段。藉此公知常识，本领域技术人员有动机尝试将证据 4 中的 β-D-2’-CH_3-胞苷/尿苷中的 2’-OH 替换为其电子等排体 2’-F 并验证其抗 HCV 效果，由此得到争议专利权利要求 1 的化合物。因此权利要求 1 相对于证据 4 与公知常识的组合不具有创造性。

5.3.2 相对于证据 4 与证据 6 的组合

证据 6 (McAtee 等 1998)公开了若干种抗病毒的 2’-氟代核苷，其中特别公开了(见证据 6 第 2161 页左栏最后一段至右栏第二段)：

> “**氟可以充当羟基的等极性类似物和电子等排类似物**，因为 C-F 键的长度(1.35Å)与 C-O 键的长度(1.43 Å)如此相似，并且因为氟是氢键受体。氟模仿羟基的能力**使氟原子独特地适合于核苷类似物来替代核苷糖部分的 OH**。除了我们对合成新颖的核苷类似物的长期持续的兴趣外，我们还有兴趣将 α-氟取代基并入糖环的 2’位置，原因有如下几点。第一，氟的电负性会使异头键稳定并抑制显著的体内降解途径，由此提高核苷的酸稳定性(图示 1)。
>
> 第二，在生物分子的体内氧化降解的第一步中，羟基常常用作“把手”。通过用 F 代替 OH，可以产生 2’位置的取代基在空间和电子上与羟基相似的类核糖，但该类核糖不能发生氧化代谢。因此，可以改进该化合物的体内半衰期”。

可见，证据 6 中明确教导了 F 和 OH 为电子等排类似物，可以在若干种抗病毒的核苷中用 F 代替 2’-α-OH 形成抗病毒的 2’-氟代核苷，这样可以提高核苷的稳定性和体内半衰期。因此，本领域技术人员在证据 4 的基础上，完全可以结合证据 6 的技术启示，得到争议专利权利要求 1 的技术方案，且其技术效果容易验

证，因此权利要求 1 不具有创造性。

5.3.3 相对于证据 4 与证据 6 和 7 的组合

在上述 5.3.2 的证据组合基础上，证据 7 (Carroll 等，2003)公开了利用 2’位置修饰的核苷类似物来抑制 HCV 的 RNA 复制，并明确公开了：

“天然底物核苷的 2’-修饰将这些分子转化为有效力的 HCV 复制抑制剂”(摘要最后一句)；

“本研究证明了 2’-取代的核苷在抑制 HCV 的 RNA 复制方面的实用性”(见 11979 页右栏最后一句)；

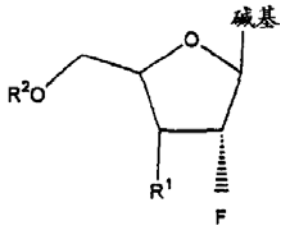
“NS5BΔ55 能够将 2’-C-甲基腺苷和 2’-O-甲基胞苷的单磷酸酯并到合适的 RNA 模板上，这表示这两种磷酸酯都能够结合到酶的底物 NTP 结合位点中，还表示在结合到该活性位点中时 2’碳和 2’氧的周围有一些额外空间，这允许 HCV NS5B 容纳 2’-C-甲基或 2’-O-甲基取代基。2’-取代基的存在可能使对病毒 RNA 聚合酶的抑制相对于对所测试的人 DNA 聚合酶的抑制具有特异性”(见第 11983 页左栏倒数第二段中部)；

“本工作确立了 2’-修饰的核苷对 HCV RNA 聚合酶活性的直接抑制导致在细胞中对 HCV 复制的抑制”(见第 11983 页右栏最后一句)。

可见，证据 7 教导了核苷的 2’位置基团对抑制 HCV 的 RNA 聚合酶 NS5B 的重要意义。而且进一步阐明了 2’-*C* 甲基腺苷能够被 NS5B 添加到 RNA 模板链末端，由此抑制 RNA 的复制，这与证据 4 的公开内容一致(证据 4 图 1 的第四个化合物即 2’-*C* 甲基腺苷)。因此，在证据 4 和 6 的基础上，结合证据 7 的进一步教导，本领域技术人员完全有动机将证据 4 的 β-D-2’-CH_3-胞苷和 β-D-2’-CH_3-尿苷中的 2’-OH 替换为 F 以得到争议专利权利要求 1 的技术方案，权利要求 1 不具有创造性。

5.3.4 相对于证据 4 与证据 8 的组合，或相对于证据 4 与证据 7 和 8 的组合

证据 8 (CN1332747A)公开了一种具有抗 HCV 效果的 2’-氟代核苷(见权利要求 10)：



其中 2'-氟处于 α 位(“下位”)，与争议专利的化合物中的氟位置相同。证据 8 还公开了：

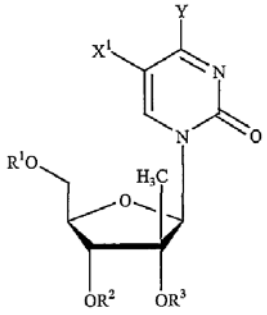
“在设计新的生物活性核苷时，人们几经尝试**将氟取代基掺入核苷的碳水化合物环中**。**将氟建议为取代基，是因为它可能作为羟基的等极和等体积的模拟物**，因为 C-F 键长(1.35 埃)与 C-O 键长(1.43 埃)非常接近，且因为氟是氢键的受体。”(参见证据 8 说明书第 5 页第 11-14 行)。

可见，证据 8 在 F 与 OH 是电子等排体的基础上，已经将核糖核苷中的 2'-OH 替换成了氟来抑制 HCV，即，证据 8 明确给出了在核苷的 2'-*C* 的 α 位采用 F 来制备抗 HCV 化合物的技术启示。

本领域公知电子等排体的相互替换是药物研发中常用的手段，因此，证据 4 与证据 8 结合可以得到权利要求 1 的技术方案，或者证据 4 与证据 7 和 8 结合也可以得到权利要求 1 的技术方案。因此，权利要求 1 不具备创造性。

以上证据涉及证据 4 的组合均可以与证据 5 中所披露的公知常识相结合。同理，权利要求 5、6、15 也不具备创造性。

此外，证据 4 在第 128-130 页公开了式 V 化合物及其具体实例，



(V)

其中，第 129-130 页的表中公开了 R^1 为单磷酸酯、二磷酸酯或三磷酸酯，R^2 为 H，R^3 为 H，X^1 为 H，Y 为 NH_2 或 OH 的所有对应实例。因此，在权利要求 1 不具备创造性的基础上，争议专利的权利要求 2-4 也不具备创造性。

此外，证据 4 在第 7 页、20 页和第 59 页都公开了包含其活性化合物的药物组合物，因此，争议专利的权利要求 7-12 和 16 也不具备创造性。

5.4 争议专利的权利要求 1-5、7-11、13-16 得不到说明书的支持

争议专利的权利要求 1 的碱基为胞嘧啶(R^4 为 NH_2)或尿嘧啶(R^4 为 OH)，即，权利要求 1 的化合物覆盖了两种核心结构不同的化合物：(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷和(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷。但是，争议专利的说明书实施例中仅公开了(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷的合成(实施例 1 和 2)和抗病毒活性(实施例 5)，并未验证权利要求 1 中的(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷及其衍生物是否已被合成、如何合成及其活性如何。因此，本领域技术人员无法得知(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷是否已经成功合成、如何合成、是否具有与(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷相同的活性。

关于化合物的合成，在争议专利的实施例 1 和 2 中制备(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷的方法中，使用了 Bz (即 C(O)Ph)与胞嘧啶上的 4 位的氨基形成酰胺结构参与合成(见实施例 1 的步骤 4 和实施例 2 的步骤 1)，而后脱去 Bz。但是，在尿嘧啶的对应位置上并非氨基，而是=O 或-OH，由于-NH_2 与-OH/=O 结构不同、性质也不完全相同，本领域技术人员不能在不实施实验的情况下推断出采用相同的方法仍能成功合成对应的(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷。

具体而言，实施例 1 的步骤 4 添加了二(三甲基甲硅烷基)-N-苯甲酰基胞嘧啶参与反应，但尿嘧啶并不具有胞嘧啶的 4-NH_2 基团，本领域技术人员不知道在该步骤中(i)尿嘧啶是否需要保护；如果需要保护，也不知道在此(ii)是否应当使用二(三甲基甲硅烷基)-N-苯甲酰基胞嘧啶的尿嘧啶类似物、(iii)使用具体如何连接保护基团的类似物以及(iv)如何制得这种类似物；即，本领域技术人员不知道在步骤 4 中应当采用何种形式的尿嘧啶才能够适应步骤 4 及后续的反应条件，更不能确信在后续反应过程中是否能够成功制得(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷以及其是否具有相同或相似的抗病毒效果。

实施例 2 的步骤 1 采用苯甲酸酐保护胞嘧啶上的 4-氨基(-NH_2)，但是尿嘧啶的 4 位并非氨基，无法受到相同的保护；而现有技术和争议专利说明书中并没有证据表明苯甲酸酐能够保护尿嘧啶的 4-OH 或 3-NH 基团，也没有证据表明尿嘧啶的 4-OH 或 3-NH 基团在争议专利实施例 2 的后续反应过程中不需要保护，因

此，本领域技术人员不知道在该步骤应该采用何种形式的尿嘧啶，更不能确信在后续反应过程中是否能够成功制得(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷以及其是否具有相同或相似的抗病毒效果。

关于化合物的效果，由于(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷与(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷是结构不同的化合物，其在穿透细胞膜进入细胞的能力方面、在细胞内所面临的降解环境方面、被各种酶(包括降解酶、失活性修饰酶和NS5B)识别的特异性和催化活性方面以及抑制 HCV 链延伸方面都可能有差异，而要达到相同的抑制 HCV 的效果，二者在这些方面(且并不限于这些方面)都必须一致或基本一致。但是，争议专利并没有任何证据表明这两种化合物在上述任一方面一致或基本一致。因此，本领域技术人员有理由怀疑(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷并不具有(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷的抗 HCV 活性。

因此，争议专利的说明书不能证明已经合成得到了(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷，本领域技术人员有理由怀疑(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷无法用相同的合成方法获得，且有理由怀疑其即使合成得到也不能实现与(2'R)-2'-脱氧-2'-氟-2'-C-甲基胞苷同样的技术效果，权利要求 1 得不到说明书的支持。

基于同样的理由，权利要求 2-5、7-11、13-16 也得不到说明书的支持。

5.5 争议专利的说明书并未充分公开权利要求 1-5、7-11、13-16 的技术方案

专利法第 26 条第 3 款规定：说明书应当对发明或者实用新型作出清楚、完整的说明，以所属技术领域的技术人员能够实现为准。

关于上述规定，《专利审查指南》第二部分第十章第 3.1 节要求，“要求保护的发明为化学产品本身的，说明书中应当记载(1)化学产品的确认、(2)化学产品的制备以及(3)化学产品的用途。”而且这三个要求需全部满足才符合第 26 条 3 款的规定。

争议专利的权利要求 1 涉及(2'R)-2'-脱氧-2'-氟-2'-C-甲基尿苷，请求人认为，该化学产品不满足上述三条要求中的任一个，不符合专利法 26.3 条的规定。

对于(1)化学产品的确认，《审查指南》第二部分第十章第 3.1 节规定：

“对于化合物发明，说明书中应当说明该化合物的化学名称及结构式(包括各种官能基团、分子立体构型等)或者分子式，对化学结构的说

明应当明确到使本领域的技术人员能确认该化合物的程度；**并应当记载与发明要解决的技术问题相关的化学、物理性能参数(例如各种定性或者定量数据和谱图等)，使要求保护的化合物能被清楚地确认**。”

但是，争议专利中仅给出了(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷的结构式，并未确认已经合成得到了该化合物，并没有给出确认其存在与否的化学、物理性能参数(例如 NMR 数据)。根据上述 5.4 节的内容，本领域技术人员根据说明书的内容也无法确认争议专利已经合成得到了(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷，因此，(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷并未得到确认。

对于(2)化学产品的制备，《审查指南》第二部分第十章第 3.1 节规定：

“对于化学产品发明，说明书中应当记载至少一种制备方法，说明实施所述方法所用的原料物质、工艺步骤和条件、专用设备等，**使本领域的技术人员能够实施。对于化合物发明，通常需要有制备实施例。**”

但是，争议专利中并没有记载(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷的具体合成方法及实施例，而且如上文 5.4 中所述，本领域技术人员根据说明书的内容也无法实施(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷的合成。因此，争议专利并没有记载(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷的具体合成方法或制备实施例，使得本领域技术人员无法合成(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷。

对于(3)化学产品的用途，《审查指南》第二部分第十章第 3.1 节规定：

“如果所属技术领域的技术人员无法根据现有技术预测发明能够实现所述用途和/或使用效果，则说明书中还应当记载对于本领域技术人员来说，足以证明发明的技术方案可以实现所述用途和/或达到预期效果的**定性或者定量实验数据**。**对于新的药物化合物或者药物组合物，应当记载其具体医药用途或者药理作用，同时还应当记载其有效量及使用方法**。”

但是，如 5.4 所述，争议专利中并没有记载足以证明(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷能够达到预期的 HCV 抑制效果的定性或者定量实验数据，而且，作为新的药物化合物(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷，争议专利也没有记载的有效量。因此，本领域技术人员不能预期(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷也能够达

到与(2’R)-2’-脱氧-2’-氟-2’-C-甲基胞苷相同或相似的技术效果。

综上，争议专利权利要求 1 的化学产品(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷及其衍生物并没有在说明书中充分公开，不符合专利法第 26.3 条的规定。同理，权利要求 2-5、7-11、13-16 也不符合专利法 26.3 的规定。

六 结论

基于上述证据和理由，权利要求 1、5-7、11、12、15、16 不具有新颖性，不符合专利法第 22 条第 2 款的规定；权利要求 1-12、15-16 不具有创造性，不符合专利法第 22 条第 3 款的规定；权利要求 1-5、7-11、13-16 得不到说明书支持，不符合专利法第 26 条第 4 款的规定；说明书并未充分公开(2’R)-2’-脱氧-2’-氟-2’-C-甲基尿苷及其衍生物，权利要求 1-5、7-11、13-16 不符合专利法第 26 条 3 款的规定。请求人恳请合议组认真考虑上述意见，宣告争议专利相关权利要求无效。

无效宣告请求人：I-MAK

Request for Announcement of Invalidation

Dear Board of Reexamination,

We, I-MAK, are writing to request for announcement of invalidation of certain claims of the Chinese patent ZL200480019148.4 (herein after referred to as “target patent”).

I. Basic information of target patent

Patent No.: 200480019148.4
Patentee upon granting: Pharmasset, Inc (New Jersey, US)
Current Patentee: Gilead Sciences, Inc
Application date: April 21, 2004
Priority date: May 30, 2003
International Application/Publication Nos.: PCT/US2004/012472 (WO 2005003147)
Applicant of international application: Pharmasset, Ltd (Barbados)
Date of grant in China: June 24, 2009
Title of invention: Modified Fluorinated Nucleoside Analogues

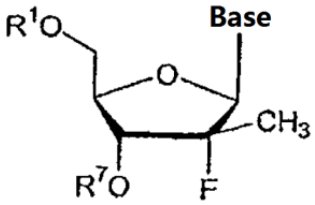
II. Evidence list

D1: WO2004002999A2;
D2: US 60/474,368;
D3: CN1761677A (D3 may also serve as a Chinese translation of D1);
D4: WO0190121A2 (CN1443191A may serve as a Chinese translation of D4)
D5: *The basic science of design on drugs*, 1995, Chen;
D6: McAtee *et al.*, A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2'-Fluoronucleosides，J. Org. Chem, 1998, 63, 2161-2167; and a Chinese translation of a part thereof;
D7: Carroll *et al.*, Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs, THE JOURNAL OF BIOLOGICAL CHEMISTRY, Vol. 278, No. 14, Issue of April 4, pp. 11979–11984, 2003; and a Chinese translation of a part thereof;

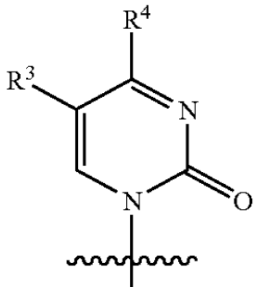
D8: CN1332747A.

III. Claims granted for target patent

1. A β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or β-L-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of the general formula below, or its pharmaceutically acceptable salt:



wherein Base is a pyrimidine base represented by the following formula



R^1 and R^7 are independently H, a C_1-C_{10} alkyl, a C_1-C_{10}alkylsulfonyl, or an arylC_1-C_{10}alkylsulfonyl, where the aryl is selected from phenyl, biphenyl or naphthyl, or R^1O- and R^7O- are independently a monophosphate, a diphosphate, a triphosphate, or a H-phosphonate; and
R^3 is H, and R^4 is NH_2 or OH.

2. The β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or β-L-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of claim 1 or its pharmaceutically acceptable salt, wherein R^7 is H and R^1O- is a monophosphate, a diphosphate, or a triphosphate.

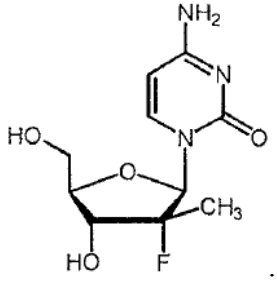
3. The β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of claim 1 or its pharmaceutically acceptable salt, R^7 is H and R^1O- is diphosphate or a triphosphate.

4. The β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or β-L-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of claim 1 or its pharmaceutically acceptable salt, wherein R^7 is H and R^1 is a triphosphate.

5. The β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside or

β-L-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of claim 1 or its pharmaceutically acceptable salt, wherein R^1 and R^7 are H.

6. A β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of the general formula below, or its pharmaceutically acceptable salt:



7. A pharmaceutical composition comprising the nucleoside of claim 1 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

8. The pharmaceutical composition comprising the nucleoside of claim 2 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

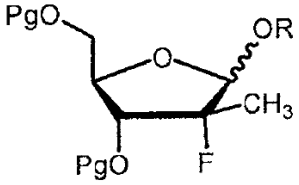
9. The pharmaceutical composition comprising the nucleoside of claim 3 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising the nucleoside of claim 4 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising the nucleoside of claim 5 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising the nucleoside of claim 6 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

13. A method of synthesizing a nucleoside of claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure;

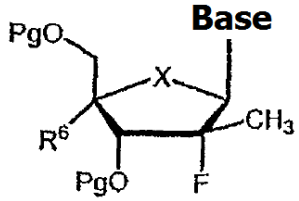


1-4

wherein R is a $C_{1\text{-}10}$ alkyl, acyl, benzoyl, or mesyl; and Pg is selected from

C(O)-C_{1-10}alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-C_{1-10}alkyl, CH_2-C_{2-6}alkenyl, CH_2Ph, CH_2-aryl, CH_2O-C_{1-10}alkyl, CH_2O-aryl, SO_2-C_{1-10}alkyl, SO_2-aryl, t-butyldimethylsilyl, t-butyldiphenylsilyl, or both Pg's may come together to form 1,3-(1,1,3,3-tetra(isopropyl)disiloxanylidene), where the aryl is selected from phenyl, biphenyl or naphthyl.

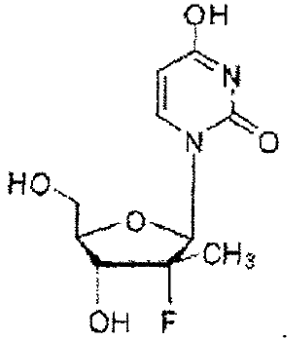
14. A method of synthesizing the nucleoside of claim 1, which comprises selectively deprotecting a 3'-OPg or a 5'-OPg of a compound having the following structure:



2-5

wherein X is O; each Pg is independently a protecting group selected from C(O)-C_{1-10}alkyl, C(O)Ph, C(O)aryl, CH_3, CH_2-C_{1-10}alkyl, CH_2-C_{2-6}alkenyl, CH_2Ph, CH_2-aryl, CH_2O-C_{1-10}alkyl, CH_2O-aryl, SO_2-C_{1-10}alkyl, SO_2-aryl, t-butyldimethylsilyl, t-butyldiphenylsilyl, or both Pg's may come together to form 1,3-(1,1,3,3-tetra(isopropyl)disiloxanylidene), where the aryl is selected from phenyl, biphenyl or naphthyl.

15. A β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl nucleoside of the general formula below, or its pharmaceutically acceptable salt:



16. A pharmaceutical composition comprising the nucleoside of claim 15 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.

IV. Facts and reasons used for this request

The facts and reasons used in this request are listed in the Table below:

Claim #	Article(s) concerned	Evidence used
1	Article 22.2	D1 or D3
1	Article 22.3	D1; D4+common knowledge; D4+D6; D4+D6+D7; D4+D8; D4+D7+D8; any of the above combinations + common knowledge
2	Article 22.3	The same as those for claim 1
3	Article 22.3	The same as those for claim 1
4	Article 22.3	The same as those for claim 1
5	Article 22.2	The same as those for claim 1
5	Article 22.3	The same as those for claim 1
6	Article 22.2	The same as those for claim 1
6	Article 22.3	The same as those for claim 1
7	Article 22.2	The same as those for claim 1
7	Article 22.3	The same as those for claim 1
8	Article 22.3	The same as those for claim 1
9	Article 22.3	The same as those for claim 1
10	Article 22.3	The same as those for claim 1
11	Article 22.2	The same as those for claim 1
11	Article 22.3	The same as those for claim 1
12	Article 22.2	The same as those for claim 1
12	Article 22.3	The same as those for claim 1
15	Article 22.2	The same as those for claim 1
15	Article 22.3	The same as those for claim 1
16	Article 22.2	The same as those for claim 1
16	Article 22.3	The same as those for claim 1
1-5, 7-11, 13-16	Article 26.4 (supportedness)	
1-5, 7-11, 13-16	Article 26.3	

V. Detailed facts and reasoning

5.1 Claims 1-12 and 15-16 of the target patent do not possess novelty or an inventive step over D1 (WO2004002999A2)

5.1.1 Validity of D1 as a prior-art document

D1 was published on Jan 8, 2004, earlier than the application date April 21, 2004 of

the target patent, and later than the priority date May 30, 2003 of the target patent. However, we believe the priority date May 30, 2003 of the target patent is invalid.

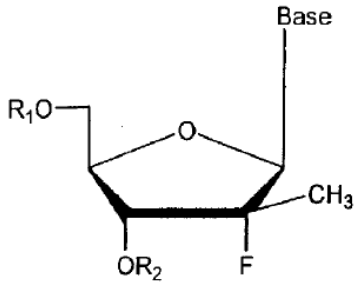
1) Article 29 of the Chinese Patent Law provides that "where, within twelve months from the date on which any applicant first filed in a foreign country an application for a patent for invention or utility model, or within six months from the date on which any applicant first filed in a foreign country an application for a patent for design, he or it files in China an application for a patent for the same subject matter, he or it may, in accordance with any agreement concluded between the said foreign country and China, or in accordance with any international treaty to which both countries are party, or on the basis of the principle of mutual recognition of the right of priority, enjoy a right of priority".

However, at the time the PCT application of the target patent was filed (April 21, 2004), its applicant was **Pharmasset, Ltd (Barbados)**, while the applicants of the prior application **US 60/474,368 (D2)** were **Jeremy Clark and Lieven Stuyer**. Until now, there is no evidence that Jeremy Clark and Lieven Stuyer assigned the right of D2 to Pharmasset, Ltd (Barbados) within 12 months from May 30, 2003. That is, the applicant of the target patent upon filing was different from the applicants of the prior application. According to the provisions of Article 29 of the Chinese Patent Law, the applicant of the target patent upon filing of the PCT (i.e. Pharmasset, Ltd (Barbados)) has no right to claim the priority of US 60/474,368. Therefore, all documents published before April 21, 2004 are prior-art documents of the target patent, and D1 is one of these valid prior-art documents.

2) The priority document D2 (US 60/474,368) does not disclose the technical solutions of claims 1-5, 7-11 and 13-16 of the target patent. Therefore, claims 1-5, 7-11 and 13-16 of the target patent cannot enjoy the priority of D2.

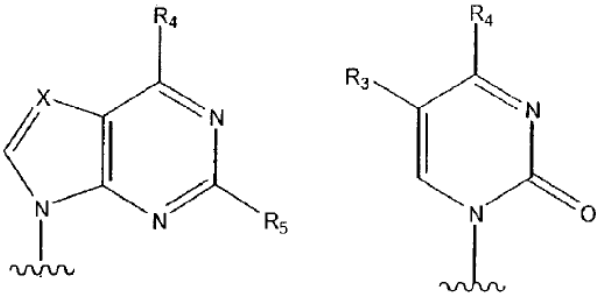
D2 discloses the following technical solution on pages 7-8:

In one embodiment, the anti-virally effective nucleoside is a β-D or β-L nucleoside of the general formula **(I)**:



(I)

wherein base can be



or its pharmaceutically acceptable salt or prodrug thereof, wherein:

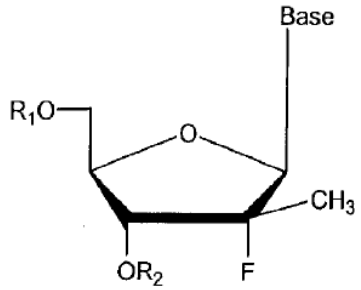
(a) X = N or CH.

(b) R1 and R2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); H-phosphonate (including stabilized H-phosphonates) acyl [including phenyl (optionally substituted), lower acyl]; alkyl (including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives); 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 R1 or R2 is independently H or phosphate. (From WO 01/90121)

(c) R3, R4 and R5 are independently H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH{=}CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH{=}CHCO_2H$, $CH{=}CHCO_2R'$;

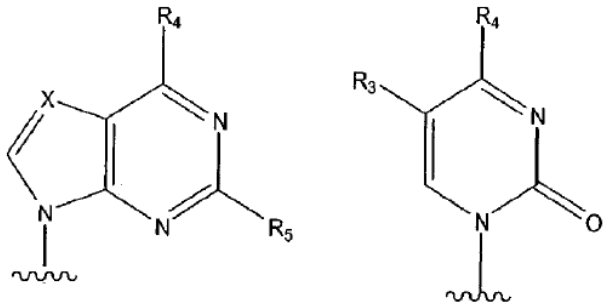
In addition, D2 discloses the following technical solution on pages 15-16:

In one embodiment, the anti-virally or anti-proliferatively effective nucleoside is a β-D or β-L nucleoside of the general formula (I):



(I)

wherein base can be



or its pharmaceutically acceptable salt or prodrug thereof, wherein:

a. X = N or CH.

b. R1 and R2 are independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); H-phosphonate (including stabilized H-phosphonates) acyl [including phenyl (optionally substituted), lower acyl]; alkyl (including lower alkyl, O-substituted carboxyalkylamino or its peptide derivatives); 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 R1 or R2 is independently H or phosphate. (From WO 01/90121)

c. R3, R4 and R5 are independently H, halogen (F, Cl, Br, I), OH, OR', SH, SR', NH_2, NHR', NR'$_2$, lower alkyl of C_1-C_6, halogenated (F, Cl, Br, I) lower alkyl of C_1-C_6 such as CF_3 and CH_2CH_2F, lower alkenyl of C_2-C_6 such as $CH=CH_2$, halogenated (F, Cl, Br, I) lower alkenyl of C_2-C_6 such as CH=CHCl, CH=CHBr and CH=CHI, lower alkynyl of C_2-C_6 such as C≡CH, halogenated (F, Cl, Br, I) lower alkynyl of C_2-C_6, lower alkoxy of C_1-C_6 such as CH_2OH and CH_2CH_2OH, CO_2H, CO_2R', $CONH_2$, CONHR', CONR'$_2$, $CH=CHCO_2H$, $CH=CHCO_2R'$;

Furthermore, D2 discloses on page 21 that:

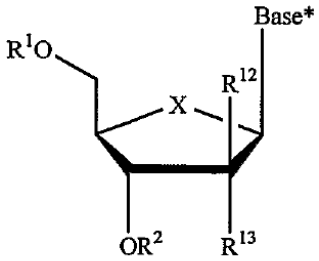
The term "lower alkyl," as used herein, and unless otherwise specified, refers to a C_1 to C_4 saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms.

In the above two technical solutions, as well as the other parts of D2, the technical solution of any of claims 1-5, 7-11 and 13-16 of the target patent is not specifically disclosed. For example only (but not limited to), D2 does not discloses R1 and R2 (corresponding to R1 and R7 in the target patent) can particularly be C_5-C_{10} alkyl, C_1-C_{10}alkylsulfonyl, or arylC_1-C_{10}alkylsulfonyl. Therefore, claims 1-5, 7-11 and 13-16 of the target patent and the technical solutions corresponding to these claims in the specification of the target patent cannot enjoy the priority of D2.

Therefore, all documents published before April 21, 2004 are prior-art documents of these claims and technical solutions concerning these claims in the target patent, and D1 is one of these valid prior-art documents of these claims and technical solutions.

5.1.2 Claims 1, 5-7, 11-12 and 15-16 of the target patent do not have novelty over D1.

D1 discloses a nucleoside analog for prevention and treatment of *Flaviviridae* infections, including HCV infection (see lines 10-13 on page 1 of D1). In particular, in lines 6-29 on page 100 of D1 (as well as claims 9-11 of D1), D1 discloses the following technical solutions:

> "In another preferred embodiment, a compound of Formula (IX), or **a pharmaceutically acceptable salt** or prodrug, or a stereoisomeric, tautomeric or polymorphic form thereof, is provided, as well as a method for the treatment of a host infected with a *Flaviviridae* comprising administering an effective treatment amount of compound of Formula (IX):
>
> 
>
>
> (IX)
>
> or a stereoisomeric, tautomeric or polymorphic form thereof, or a pharmaceutically acceptable salt thereof, wherein:
> R^1, R^2 and R^3 are independently **H; phosphate**; straight chained, branched or cyclic **alkyl**; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; **alkylsulfonyl**; arylsulfonyl; **aralkylsulfonyl**; a lipid; an amino acid; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;
> X is O, S, SO_2 or CH_2;
> Base* is a purine or pyrimidine base;
> R^{12} is $C(Y^3)_3$;
> Y^3 is independently H, F, Cl, Br or I; and
> R^{13} is fluoro.
>
> In one subembodiment **X is O, and Y_3 is H**. In another subembodiment, when X is O and Y^3 is H, **R^1, R^2 and R^3 are also H**."

In the above first subembodiment (**Subemb I**), X is O, R^{12} is methyl, the base is a purine or pyrimidine base, R^1 and R^2 (corresponding to R^1 and R^7 in claim 1 of the

target patent, respectively) may be H, phosphate, alkyl, alkylsulfonyl, or aralkylsulfonyl.

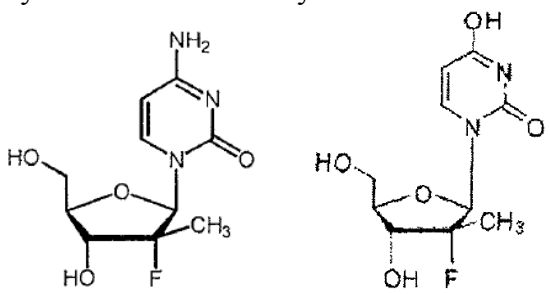
In the above second subembodiment (**Subemb II**), X is O, R^{12} is methyl, the base is a purine or pyrimidine base, R^1 and R^2 are both H.

In addition, the ***Definitions*** section of D1 discloses:

> The term "alkyl", as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of **typically C_1 to C_{10}** (lines 12-14 on page 103);
>
> The term "aryl", as used herein, and unless otherwise specified, refers to **phenyl, biphenyl, or naphthyl** (lines 3-4 on page 104);
>
> The term "purine" or "pyrimidine" base includes, but is not limited to, adenine… thymine, **cytosine**, …, **uracil**, … (from line 15 on page 104);

Furthermore, the compounds of the invention of D1 are all 2' and 3'-prodrugs of **nucleosides** (lines 12 on page 12 of D1). It is well known in the art that in natural cytosine nucleoside (cytidine) and uracil nucleoside (uridine), the cytosine and uracil bases are both linked to the sugar ring with their N_1 atom. Therefore, for the Base* in formula (IX), Subemb I and Subemb II of D1 in fact disclose cytosine and uracil bases linked to the sugar ring with their N_1 atom, which are exactly the "Base" in claim 1 of the target patent.

Hence, Subemb II of D1 discloses "β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine" and "β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine":



which completely fall within the scope of claim 1 of the target patent (corresponding to the case where R^1=R^7=H). Hence, claim 1 of the target patent does not have novelty. Similarly, claims 5, 6 and 15 also do not have novelty.

D1 further discloses pharmaceutical compositions comprising the nucleosides of D1 and pharmaceutically acceptable salts thereof on page 44 (e)-(g), discloses pharmaceutical compositions comprising the active ingredients or pro-drugs of D1 or salts thereof on page 117, and also discloses that an object of D1 is to provide a composition for treatment of HCV infection in lines 6-7 on page 12.

Therefore, since claims 1, 5, 6 and 15 lack novelty, claims 7, 11, 12 and 16 also lack novelty since their additional technical features are disclosed in D1.

5.1.3 Claims 1-12 and 15-16 of the target patent do not have an inventive step over D1.

Claim 1 of the target patent does not have an inventive step over Subemb I of D1, because a person skilled in the art would have conventionally chosen R^1 and R^2 in formula (IX) (corresponding to R^1 and R^7 in claim 1 of the target patent, respectively) as H, a $C_{1\text{-}10}$ alkyl, a C_1-C_{10}alkylsulfonyl, an arylC_1-C_{10}alkylsulfonyl, where the aryl is selected from phenyl, biphenyl or naphthyl, or a phosphate, based on the above disclosure of Subemb I of formula (IX) and definitions of groups in D1 (see particularly the underlined parts above).

Furthermore, it is a conventional choice to select a diphosphate or a triphosphate on the 5'-position of a nucleoside, because it is well known to a person skilled in the art that the unit participating in DNA/RNA synthesis is triphosphate nucleoside, which originates from the unphosphorylated nucleoside though stepwise phosphorylation via monophosphate and diphosphate. Hence, since claim 1 does not have an inventive step, claims 2-4 also lack an inventive step.

D1 has disclosed the additional technical features of claims 5 and 6, and thus claims 5-6 do not have an inventive step.

Based on the disclosure about pharmaceutical compositions in D1 (see 5.1.2 above), claims 7-10 do not have an inventive step.

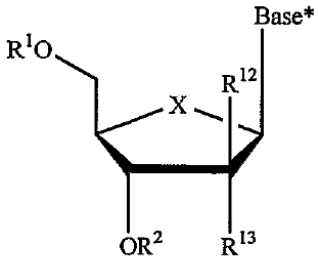
Based on the disclosure about pharmaceutical compositions in D1 (see 5.1.2 above), claims 11-12 also do not have an inventive step.

Since claims 15-16 do not have novelty (see 5.1.2), they also lack an inventive step.

5.2 Claims 1, 5-7, 11-12 and 15-16 of the target patent does not possess novelty over D3 (CN1761677A)

D3 is the national-phase application of D1 in China, whose priority dates are June 28, 2002, April 28, 2003, and May 14, 2003, all of which are earlier than the priority date April 21, 2004 (or May 30, 2003 even if the priority claim of the target patent is valid) of the target patent. D3 is disclosed on April 19, 2005, later than the priority date of the target patent. Therefore, D3 is a conflicting application to the target patent and can be used to evaluate the novelty of the claims of the target patent.

D3 discloses the following technical solutions on pages 74-75 of its specification:

> "In another preferred embodiment, a compound of Formula (IX), or **a pharmaceutically acceptable salt** or prodrug, or a stereoisomeric, tautomeric or polymorphic form thereof, is provided, as well as a method for the treatment of a host infected with a *Flaviviridae* comprising administering an effective treatment amount of compound of Formula (IX):
>
> 
>
>
> (IX)
>
> or a stereoisomeric, tautomeric or polymorphic form thereof, or a pharmaceutically acceptable salt thereof, wherein:
> R^1, R^2 and R^3 are independently **H; phosphate**; straight chained, branched or cyclic **alkyl**; acyl; CO-alkyl; CO-aryl; CO-alkoxyalkyl; CO-aryloxyalkyl; CO-substituted aryl; sulfonate ester; benzyl, wherein the phenyl group is optionally substituted with one or more substituents; **alkylsulfonyl**; arylsulfonyl; **aralkylsulfonyl**; a lipid; an amino acid; a carbohydrate; a peptide; cholesterol; or a pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1, R^2 and/or R^3 is independently H or phosphate;
> X is O, S, SO_2 or CH_2;
> Base* is a purine or pyrimidine base;
> R^{12} is $C(Y^3)_3$;
> Y^3 is independently H, F, Cl, Br or I; and

R^{13} is fluoro.

In one subembodiment **X is O, and Y_3 is H**. In another subembodiment, when X is O and Y^3 is H, **R^1, R^2 and R^3 are also H**."

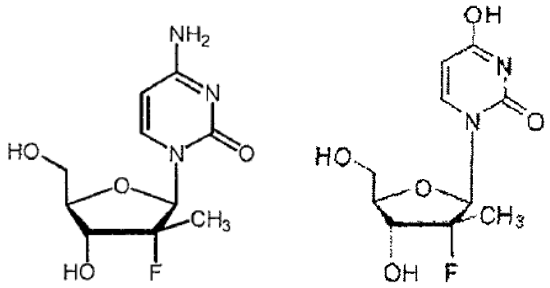
In the above second subembodiment (Subemb II), X is O, R^{12} is methyl, the base is purine or pyrimidine base, R^1 and R^2 are both H.

In addition, the ***Definitions*** section of D3 discloses:

The term "purine" or "pyrimidine" base includes, but is not limited to, adenine… thymine, **cytosine**, …, **uracil**, … (on page 77);

Furthermore, the compounds of the invention of D3 are all 2' and 3'-prodrugs of **nucleosides** (lines 2 on page 9 of D3). In is well known in the art that in natural cytosine nucleoside (cytidine) and uracil nucleoside (uridine), the cytosine and uracil bases are both linked to the sugar ring with their N_1 atom. Therefore, for the Base* in formula (IX), Subemb II of D3 in fact discloses cytosine and uracil bases linked to the sugar ring with their N_1 atom, which are exactly the "Base" in claim 1 of the target patent.

Hence, Subemb II of D3 in fact discloses "β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine" and "β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine":



both of which completely fall within the scope of claim 1 of the target patent (corresponding to the case where R^1=R^7=H). Hence, claim 1 of the target patent does not have novelty. Similarly, claims 5, 6 and 15 also do not have novelty.

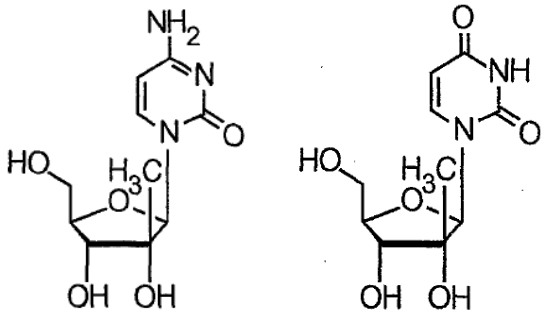
D3 further discloses pharmaceutical compositions comprising the nucleosides of D3 and pharmaceutically acceptable salts thereof on page 32 (e)-(g), discloses pharmaceutical compositions comprising the active ingredients or pro-drugs of D3 or salts thereof on page 86, and also discloses that an object of D3 is to provide a composition for treatment of HCV infection in the second last paragraph on page 8.

Therefore, for the same reasons commented in **5.1.2** above, claims 1, 5-7, 11-12 and 15-16 of the target patent lack novelty over D3.

5.3 Claims 1-12 and 15-16 of the target patent do not possess an inventive step over D4 (WO0190121A2) or over the combination of D4 with other evidence(s)

5.3.1 Regarding D4 in combination with common knowledge

D4 discloses a series of anti-HCV nucleoside compounds (see the last paragraph on page 20 of D4), and particularly discloses two compounds β-D-2'-CH_3-cytidine and β-D-2'-CH_3-uridine in Figure 1:



which differ from the β-D-(2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine/uridine of claim 1 of the target patent only in that its 2'-*C* position has an α-OH group while its counterpart in claim 1 of the target patent is F. Based on this distinguishing feature, the technical problem to be practically solved by the invention of claim 1 of the target patent is how to provide new anti-HCV nucleosides.

D5 (*The basic science of design on drugs*, 1995, Chen, a textbook) discloses that F and OH are biological isosteres (see the "Monovalent isosteres" in Table 8-6 on page 162 of D5). It is well known to a person skilled in the art that in design and development of drugs isosteres are exchangeable and may produce similar technical effects (see lines 1-2 on page 164 of D5). Therefore, it is common knowledge that replacement between isosteres is a routine and conventional means used in drug design and development. With this common knowledge, a person skilled in the art would be motivated to try to replace the 2'-OH in the β-D-2'-CH_3-cytidine/uridine disclosed in D4 with its isostere fluorine and to test its anti-HCV potency, so as to obtain the compounds of claim 1 of the target patent.

Hence, claim 1 does not have an inventive step over D4 in combination with common knowledge.

5.3.2 Regarding D4 in combination with D6

D6 (McAtee, *et al.*, 1998) discloses several antiviral 2'-fluoronucleosides, and particularly discloses (see the last paragraph in the left column to the second paragraph in the right column on page 2161 of D6):

> "**Fluorine** may also serve as an isopolar and **isosteric mimic of a hydroxyl group** since the C-F bond length (1.35 Å) is so similar to the C-O bond length (1.43 Å) and because fluorine is a hydrogen-bond acceptor. The ability of fluorine to mimic a hydroxyl group makes this atom **uniquely suited to nucleoside analogues as a replacement of OH in the sugar portion of a nucleoside**. In addition to our long standing interest in the synthesis of novel nucleoside analogues, we were interested in incorporating an α-fluorine substituent at the 2' position of the sugar ring for several reasons. First, the electronegativity of fluorine should stabilize the anomeric bond and suppress a significant pathway of *in vivo* decomposition, thereby improving the acid stability of the nucleoside (Scheme 1).
> Second, hydroxyl groups often serve as "handles" for the first step in oxidative degradation of biomolecules *in vivo*. By replacing OH with F, it is possible to create a ribo-like sugar that has a substituent at the 2' position sterically and electronically similar to a hydroxyl group, but which cannot undergo oxidative catabolism. Thus, the *in vivo* half-life of the compound may be improved."

It can be seen that D6 explicitly teaches that F and OH are isosteres, and the 2'-α-OH in antiviral nucleosides can be replaced with F to obtain several antiviral 2'-fluoronucleosides, such that the stability and *in vivo* half-life of the nucleosides can be improved. Therefore, on the basis of D4, a person skilled in the art would be taught by D6's technical inspiration to obtain the compounds of claim 1 of the target patent, and the technical effects thereof are easy to verify. Hence, claim 1 of the target patent does not have an inventive step.

5.3.3 Regarding D4 in combination with D6 and D7

Based on the combination of evidences in 5.3.2, D7 (Carroll *et al.*, 2003) further discloses use of 2'-modified nucleoside analogs to inhibit HCV RNA replication (see the title of D7), and explicitly discloses:

> "the 2'-modifications of natural substrate nucleosides transform these

molecules into potent inhibitors of HCV replication" (see the last sentence of the Abstract);

"this study demonstrates the utility of 2'-substituted nucleosides in the inhibition of HCV RNA replication" (see the last sentence in the right column on page 11797 of D7);

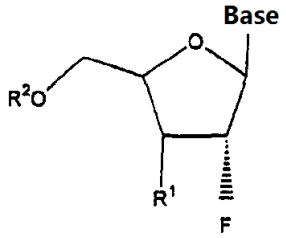
"NS5BΔ55 is capable of incorporating both 2'-*C*-methyladenosine monophosphate and 2'-*O*-methylcytidine monophosphate onto the appropriate RNA template, implying that both triphosphates can bind to the enzyme in the substrate NTP binding site and further implying there is some additional room in the vicinity of the 2'-carbon and the 2'-oxygen when bound in the active site that allows HCV NS5B to accommodate either the 2'-C-methyl or 2'-O-methyl substituent. The presence of 2'-substituents likely confers specificity of inhibition of the viral RNA polymerase over inhibition of the human DNA polymerases tested" (see the middle part of the second last paragraph in the left column on page 11983 of D7);

"the current work establishes the direct inhibition of HCV RNA polymerase activity by 2'-modified nucleotides leading to inhibition of HCV replication in cells" (the last sentence in the right column on page 11983 of D7).

Therefore, D7 teaches the significance of 2'-substituents of nucleosides for inhibition of HCV RNA replication by RNA polymerase NS5B, and further illustrates that 2'-*C*-methyladenosine can be added to the terminal of the RNA template by NS5B, to inhibit RNA replication, which is consistent with the disclosure of D4 (the fourth compound in Figure 1 of D4 is 2'-*C*-methyladenosine). Based on the combination of D4, D6, and further D7, a person skilled in the art would be fully motivated to obtain the technical solution of claim 1 of the target patent. Hence, claim 1 of the target patent does not have an inventive step.

5.3.4 Regarding D4 in combination with D8, or D4 in combination with D7 and D8

D8 (CN1332747A) discloses an anti-HCV 2'-fluoronucleoside (see claim 10 thereof):



wherein the 2'-fluorine is at the α position ("down" position), the same as in the compounds of the target patent. D8 further discloses:

> "In designing new biologically active nucleosides, there have been a number of attempts to **incorporate a fluoro substituent into the carbohydrate ring of the nucleoside**. **Fluorine has been suggested as a substituent because it might serve as an isopolar and isosteric mimic of a hydroxyl group** as the C-F bond length (1.35 Å) is so similar to the C-O bond length (1.43 Å) and because fluorine is a hydrogen bond acceptor" (see lines 11-14 on page 5 of D8).

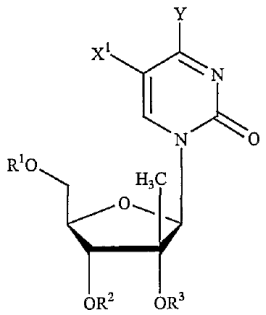
Therefore, based on the common knowledge that F and OH are isosteres, D8 has practically replaced the 2'-α-OH in nucleosides with fluorine to produce new HCV inhibitors. That is, D8 has clearly taught using F at the 2'-α-position to produce anti-HCV nucleosides.

Since it is common knowledge in the art that isosteric replacement is a conventional technical means in drug design and development, claim 1 of the target patent would have been easily obtained based on D4 in combination with D8, or based on D4 in combination with D7 and D8. Hence, claim 1 of the target patent does not have an inventive step.

Each of the above combinations involving D4 can be further combined with the common knowledge disclosed in D5 to disprove the inventiveness of claim 1.

Since claim 1 has no inventiveness, claims 5, 6 and 15 also have no inventiveness.

Furthermore, D4 discloses formula V and its examples on pages 128-130:



(V)

wherein the Table over pages 129-130 discloses examples where R^1 is monophosphate, diphosphate, or triphosphate; R^2 is H; R^3 is H; X^1 is H; Y is NH_2 or OH, in each and every combination. Therefore, since claim 1 does not have inventiveness, claims 2-4 also lack inventiveness.

In addition, D4 discloses pharmaceutical compositions comprising the active compounds on pages 7, 20 and 50. Therefore, claims 7-12 and 16 also do not have inventiveness.

5.4 Claims 1-5, 7-11 and 13-16 of the target patent are not supported by the specification

Claim 1 of the target patent actually includes (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine (R^4 is NH_2) and uridine (R^4 is OH), which are two different compounds having different core structures. However, the specification and Examples of the target patent only disclose the synthesis of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine (Examples 1 and 2) and its antiviral activity (Example 5), but does not verify the compound (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine in claim 1 in terms of whether it had been synthesized, how it was synthesized and how active it was. Therefore, a person skilled in the art would not know whether (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine had been successfully synthesized, how it was synthesized, or whether it had the same or similar activity as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

About the synthesis of the compound, in the synthesis method for (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine in Examples 1 and 2 of the target patent, Bz (i.e. C(O)Ph) was used to form an amide structure with the 4-NH_2 on cytosine to participate in the synthesis (see Step 4 of Example 1 and Step 1 of Example 2), and later removed. However, uracil does not have a -NH_2 group at the corresponding

position, but a =O or –OH which is different form -NH_2 in structure and properties, and a person skilled in the art cannot be sure, without carrying out experiments, that the method for the cytidine can also be used to successfully synthesize the uridine.

Specifically, Step 4 of Example 1 added bis(trimethylsilyl)-N-benzoylcytosine in the reaction for the cytidine. However, since uracil does not have the 4-NH_2 as in cytosine, a person skilled in the art does not know in this step (i) whether uracil needs a protecting group, and if a protecting group is need, he does not know (ii) whether a uracil derivative similar to bis(trimethylsilyl)-N-benzoylcytosine should be used, (iii) how the bis(trimethylsilyl) or other protecting group is linked to uracil, or (iv) how to synthesize or obtain this uracil derivative. That is, a person skilled in the art would not know what form of uracil should be used in Step 4 to adapt to the reaction conditions in Step 4 and subsequent steps, let alone predict whether (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can be successfully synthesized at the end of the process and whether it has the same or similar antiviral effect as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

Step 1 of Example 2 used benzoic anhydride to protect the 4-NH_2 group on cytosine. However, uracil cannot be protected in the same way because of lack of 4-NH_2. In the prior art and the specification of the target patent, there is no evidence that benzoic anhydride can protect the 4-OH or 3-NH group of uracil, nor evidence that the 4-OH or 3-NH group of uracil does not need protection in subsequent process of Example 2. Therefore, a person skilled in the art would not know what form of uracil should be used in Step 1 of Example 2, let alone predict whether (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can be successfully synthesized at the end of the method and whether it has the same or similar antiviral effect as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

About the effects of the compound, because (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine is structurally different from (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine, they may be different in terms of the ability to penetrate the cell membrane, the degradation environments in the cell they face, the specificity and catalytic activity of various enzymes (including the degradation enzymes, inactivating modifying enzymes and NS5B) against them, and the ability to terminate chain elongation of HCV. In order to have the same or substantially same anti-HCV effects, the two must be the same or substantially same in all of (but not limited to) the above aspects. However, the target patent fails to provide any evidence that these two compounds are the same or substantially same in any of the above aspects. Therefore, a person skilled

in the art has reason to doubt that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has the anti-HCV activity of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

Hence, the specification of the target patent fails to demonstrate that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine had been successfully synthesized by the priority date. A person skilled in the art has reason to doubt that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can be practically synthesized following the method for cytidine, and also has reason to doubt that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine, even if it exists, has the same or similar technical effect as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine. Claim 1 of the target patent is not supported by the specification.

For the same reason, claims 2-5, 7-11 and 13-16 of the target patent are also not supported by the specification.

5.5 The specification of the target patent fails to sufficiently discloses the technical solutions of Claims 1-5, 7-11 and 13-16

Article 26.3 of the Chinese Patent Law provides that "the description shall set forth the invention or utility model in a manner sufficiently clear and complete so as to enable a person skilled in the relevant field of technology to carry it out".

With regard to the above provision, *The Guideline of Patent Examination* requires in Section 3.1, Chapter 10, Part II that "where the claimed invention is a chemical product itself, the description shall describe the **(1) identification, (2) preparation and (3) use of the chemical product**", which require all the three must be met to conform to Article 26.3.

Claim 1 of the target patent involves (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine, which we believe does not meet any of the above three requirements, and claim 1 does not conform to the provisions of Article 26.3 of the Chinese Patent Law.

About (1) identification of a chemical product, Section 3.1, Chapter 10, Part II of *The Guideline of Patent Examination* requires:

> "As for the invention of a compound, the description shall indicate the chemical name and the structural formula (including various function groups, molecule steric-configuration and so on) or the molecular formula of said compound. The explanation of the chemical structure shall be clear

enough to enable a person skilled in the art to identify the compound. **In order to clearly identify the claimed compound, the description shall describe the chemical/physical property parameters (such as the various qualitative or quantitative data and spectrum, etc.) relating to the technical problem to be solved by the invention.**"

However, the specification of the target patent only provides the chemical formula of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine, but neither confirms whether this compound has been successfully obtained, nor provides chemical/physical property parameters (like NMR data) to identify this compound. Based on the observations in **5.4** above, a person skilled in the art, based on the specification, cannot be sure that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has been successfully synthesized in the target patent. Therefore, (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine is not identified in the target patent.

About (2) preparation of a chemical product, Section 3.1, Chapter 10, Part II of *The Guideline of Patent Examination* requires:

"The description of a chemical product invention shall describe at least one preparation method and disclose the **raw materials**, procedures, **conditions** and specially adapted equipment used for carrying out the method so as to make it possible for a person skilled in the art to carry it out. **In the case of a compound invention, the example of its preparation is usually required**".

However, the specification of the target patent does not provide a specific synthesis method or preparation example for (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. And as observed above, the target patent fails to disclose the specific uracil/uridine-based raw material and corresponding conditions for synthesis of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. Therefore, a person skilled in the art based on the specification cannot carry out preparation of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. Hence, the specification of the target patent does not disclose any specific synthesis method or preparation example for (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine, and fails to enable a person skilled in the art to synthesis (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine.

About (3) use of a chemical product, Section 3.1, Chapter 10, Part II of *The Guideline of Patent Examination* requires:

"If a person skilled in the art is unable, on the basis of the prior art, to

predict that the use and/or its technical effect stated in the invention can be carried out, the description shall sufficiently provide **qualitative or quantitative data of experimental tests** for the person skilled in the art to be convinced that the technical solution of the invention enable the use to be carried out and/or the effect as expected to be achieved.
For a new pharmaceutical compound or pharmaceutical composition, not only its specific medical use or pharmacological action, but also its effective amount and the method of application shall be described"

However, as described in 5.4, the specification of the target patent does not disclose any qualitative or quantitative data or experimental tests that are sufficient to prove that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can produce an expected anti-HCV effect. Furthermore, as a new compound, the target patent does not provide an effective amount for (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. Therefore, a person skilled in the art is unable to predict that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can product the same or similar effect as (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine.

In summary, the new compound (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine in claim 1 of the target patent is not sufficiently disclosed in the specification, which does not conform to the provisions of Article 26.3 of the Chinese Patent Law.

By the same token, claims 2-5, 7-11 and 13-16 also do not conform to the provisions of Article 26.3 of the Chinese Patent Law.

VI. Conclusion

Based on the above evidence and reasons, claims 1, 5-7, 11-12 and 15-16 of the target patent do not have novelty as required by Article 22.2 of the Chinese Patent Law; claims 1-12 and 15-16 do not have inventiveness as required by Article 22.3 of the Chinese Patent Law; claims 1-5, 7-11 and 13-16 are not supported by the specification, and do not conform to the provisions of Article 26.4 of the Chinese Patent Law; and claims 1-5, 7-11 and 13-16 are not sufficiently disclosed by the specification, and do not conform to the provisions of Article 26.3 of the Chinese Patent Law. We sincerely request the Board of re-examination to consider the above observations and announce invalidation of the above claims of the target patent.

Petitioner: I-MAK

Request for Announcement of Invalidation
Supplemental Observations

Dear Board of Reexamination,

We, I-MAK, filed the request for announcement of invalidation of certain claims of the Chinese patent ZL200480019148.4 (hereinafter referred to as "target patent") on April 19, 2017, and are now writing to file supplemental evidences and observations to support our previous observations.

I. Basic information of target patent

Patent No.: 200480019148.4
Patentee upon granting: Pharmasset, Inc (New Jersey, US)
Current Patentee: Gilead Sciences, Inc
Application date: April 21, 2004
Priority date: May 30, 2003
International Application/Publication Nos.: PCT/US2004/012472 (WO 2005003147)
Applicant of international application: Pharmasset, Ltd (Barbados)
Date of grant in China: June 24, 2009
Title of invention: Modified Fluorinated Nucleoside Analogues

II. New Evidence List

D9: Herdewijn *et al.*, (1989);
D10: Matsuda *et al.*, (1987);
D11: Wagner *et al.*, (2000);
D12: Michael *et al.*, (1998);
D13: Clark *et al.*, (2005);
D14: Gilead's defense observations filed in the opposition against EP2203462B in EPO, accessible via the official web site of EPO: https://register.epo.org/application?number=EP08732818&lng=en&tab=doclist, in which page the second document updated on Dec 11, 2005, named "Reply of the patent proprietor to the notice(s) of opposition" (pages 114) is D14.

III. Claims granted for target patent (omitted)

IV. Facts and reasons used for this request (New)

The new facts and reasons used in this request are listed in the Table below, which are only in addition to, not replacement of, the previous facts and reasons:

Claim #	Article(s) concerned	Evidence used
1	Article 22.3	D1; D4+common knowledge; D4+D6; D4+D6+D7; D4+D8; D4+D7+D8; any of the above combinations + common knowledge; **any of the above combinations + D9+D10** **any of the above combinations + D6+D9+D10**
2-12, 15-16	Article 22.3	The same as those for claim 1

V. Detailed facts and reasoning (supplemental)

S1. Supplemental observations to Section 5.3 of our previous observations

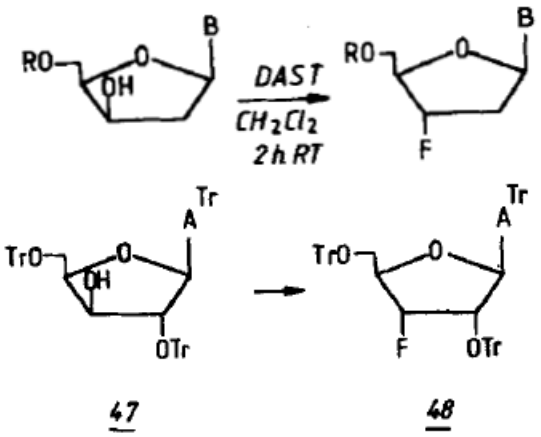
As observed in Section 5.3, a person skilled in the art would be motivated to replace the 2'-OH ("down") in the nucleoside analogs disclosed in D4 with a fluorine atom. Based on this, in order to synthesize the target product having the 2'-F ("down"), a person skilled in the art would be motivated and able to use DAST (diethylaminosulfur trifluoride) to treat a corresponding nucleoside having a 2'-OH("up")-2'-CH_3("down") configuration to obtain the target product having the 2'-F ("down")-2'-CH_3("up") configuration based on the teaching of D6, D9 and/or D10.

D6 discloses that "Fluorine is **usually** introduced into these molecules through nucleophilic attack on an anhydro-nucleoside or through **replacement and inversion** of a stereochemically fixed hydroxyl group with diethylaminosulfur trifluoride (DAST)" in lines 4-9 of the right column on page 2163, which explicitly indicates that DAST has an effect of replacing hydroxyl with fluorine in a configuration-inversing manner.

D9 (Herdewijn *et al.*) discloses such replacement and inversion effect of DAST. D9 in lines 4-5 of the second last paragraph on page 80 discloses "This reagent (DAST) has

been successfully applied for the replacement of a hydroxyl group by a fluorine atom", and in lines 1-2 of the last paragraph on page 80 discloses "The reaction with DAST affords products resulting from Walden inversion". It is well known in the art that Walden inversion refers to configuration inversion of the group on a chiral carbon atom. In other words, after replacement of OH with F by using DAST, the configuration of F on the chiral carbon atom is reversed relative to that of the hydroxyl group.

Furthermore, D9 discloses a couple of examples for such reactions with DAST on pages 81 and 85:

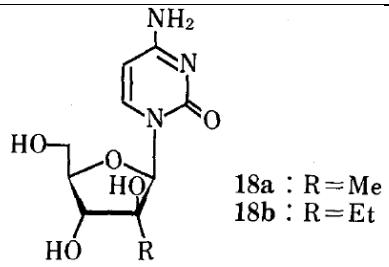


47 48

In addition, in the synthesis of 48, protective groups were used to protect hydroxyl groups that were not to be replaced with F.

Therefore, based on the teachings of D6 and D9, in order to obtain (2'R)-2'-deoxy-2'-fluoro("down")-2'-*C*-methyl("up") cytidine, a person skilled in the art would be motivated and able to use DAST to treat a corresponding nucleoside having a 2'-OH("up")-2'-CH_3("down") configuration, with necessary protective groups on the hydroxyl groups not to be replaced with F, so as to obtain the target product.

The corresponding nucleoside having a 2'-OH("up")-2'-CH_3("down") configuration, as well as its synthesis, has been disclosed in D10 (Matsuda *et al.*) (see Compound 18a on page 949 of D10).



18a : R=Me
18b : R=Et

In summary, under the teaching of D6, D9 and D10, a person skilled in the art would be fully motivated and able to use DAST to treat Compound 18a of D10, to achieve the replacement of OH with F of the compound disclosed in D4, so as to obtain the claimed compound of the target patent. And implementation of such a process has no technical obstacles to overcome.

S2. Supplemental observations to Sections 5.4 and 5.5 of our previous observations

S2.1 The mechanism by which nucleoside analogs inhibit viral nucleic acid polymerases

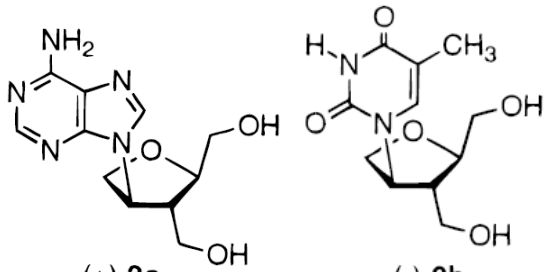
It is well known in the art that viral replication in a host cell involves: stepwise conversion of a nucleoside (N=A, U/T, G or C) by intracellular kinases into 5'-triphosphate of the nucleoside (NTP) which is the building block of DNA/RNA, recognition of the NTP by viral DNA/RNA polymerase, and subsequent synthesis of viral DNA/RNA. Based on this mechanism, nucleoside analogs (N') have been developed as antiviral drugs, in which case N' enters the cell through the cell membrane, is recognized by intracellular kinases (of the virus or the host) to turn into N'TP, which competes with natural NTPs for recognition by viral DNA/RNA polymerase and for incorporation into the viral DNA/RNA chain, and terminates chain elongation by its difference from natural NTPs, so as to achieve inhibition (see the first two paragraphs of the "Introduction" section and Figure 1 of D11 (Wagner *et al.*), and also see the Abstract of D7). The nucleosides claimed by the target patent also follow the above mechanism.

Therefore, for a new nucleoside analog to have effective antiviral activity of inhibiting viral nucleic acid polymerase, it must show similar or higher rates in all the above steps, i.e. cell membrane penetration, monophosphorylation, diphosphorylation, triphosphorylation, incorporation into the nucleic acid chain, and inhibition of chain elongation, and meanwhile the degradation of the nucleoside analog, as well as any

other intermediates, by other enzymes in the cell must be slow enough. These require experiments to investigate and verify. However, the target patent only verified the anti-HCV activity of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine, and based on this result, a person skilled in the art would not see that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine can also penetrate the cell membrane, be phosphorylated into NTP, and be incorporated into the chain at rates that do not significantly affect the final inhibitory activity.

S2.2 Nucleoside analogs differing only in the base do not necessarily have the same or similar inhibitory activity, and may even have no activity

As a support to the conclusion in S2.1, D12 (Michael 1998) discloses a series nucleoside analogs for antiviral (e.g. anti-HIV) purposes, which also follow the mechanism described in S2.1 above (see lines 3-6 on page 347 of D12). That is, they enter the cell, turn into triphosphate, and are incorporated into the chain to terminate the elongation. The results of D12 show that, among these analogs, L-(+)-2a was inactive to inhibit HIV, while L-(-)-2b showed moderate anti-HIV activity (see the second last paragraph on page 349 of D12).



The structures of L-(+)-2a and L-(-)-2b are shown above (see Scheme 4 of D12) and it can be seen that they differ only in the base: adenosine for L-(+)-2a and thymine for L-(-)-2b. Both adenosine and thymine are bases in viral DNA, but these two analogs show significantly different antiviral activity. This further validates the conclusion that nucleoside analogs that differ only in base do not necessarily have the same or similar antiviral activity against the same virus, and some of them may even have no activity at all.

S2.3 The target patent did not do any work on (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine by the priority date.

D13 (the first author thereof is the first inventor of the target patent, Jeremy Clark) discloses that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine (Compound 9 of D13)

showed no activity against HCV (see the first paragraph of the right column on page 5506 and Table 2 of D3), while (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine (Compound 1 of D13) in the same assay showed apparent activity. This result also verifies the conclusion of S2.1 above, that is, based on the positive activity of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl cytidine, a person skilled in the art cannot infer that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has the same, similar or even any activity. It could rather have no activity like L-(+)-2a in D12. D3 also proves that the activity of (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine was not investigated at all by the patentee when the patent application was filed, that is, the patentee did not make any technical contribution over the prior art regarding (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine. Therefore, the technical solutions related to (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine were not sufficiently disclosed in the target patent, nor supported by the specification of the target patent.

Furthermore, D14, the observations filed by the patentee of the target patent in EPO (in an opposition procedure against another related patent), shows that the patentee admits that they did not know whether (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has anti-HCV activity at the priority date of the target patent. D14 includes several statements made by Gilead:

◆ 12.40 on page 65: Clark 2005 reported that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine (Compound 9) showed no activity against HCV;

◆ 12.45 on page 67: It was not known in 2007 why the compound ((2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine) showed no activity. There were many possible reasons for this inactivity, including poor uptake into the cell; fast metabolization of the nucleoside; no or slow intracellular phosphorylation to the mono-, di- or triphosphate; and fast metabolization of any of those phosphate compounds.

From the above observations made by Gilead, they have admitted that:

1) By the date of filing (or priority date) of the target patent, the patentee or inventor did not know whether (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has anti-HCV activity, because later on they found that the uridine analog has no activity; and

2) There were many possible reasons for this inactivity, and the exact reason was not known by at least 2007, that is, by 2007 there was no known technical solution that can make (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine active.

Therefore, by the priority date of the target patent, and even until 2007, a person skilled in the art cannot predict that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has

anti-HCV activity, and also cannot resolve this inactivity by known technical means in the art or the contents disclosed in the target patent. That is, a person skilled in the art has sufficient reason to doubt that (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine has anti-HCV activity. In conclusion, the technical solutions related to (2'R)-2'-deoxy-2'-fluoro-2'-*C*-methyl uridine were not sufficiently disclosed in the target patent, nor supported by the specification of the target patent.

Petitioner: I-MAK