Dear Examiner,

According to the provisions of Rule 48 of the Implementing Regulations of the Chinese Patent Law, any person may, from the date of publication of an application for a patent for invention till the date of announcing the grant of the patent right, submit to the patent administration department under the State Council his observations, together with reasons, on the application which is not in conformity with the provisions of the Chinese Patent Law.

Now, according to the above provisions, here we are making observations against the following Chinese patent application (hereinafter referred to as the “target application”) which we believe does not conform to the provisions on patentability in the Chinese Patent Law and therefore should not be patented.

**Basic information of the target application:**
- Application No.: CN 200880018024.2
- PCT Application No.: PCT/US2008/058183
- PCT Publication No.: WO2008/121634
- Filing date: March 26, 2008
- Priority date (the earliest): March 30, 2007
- Title of the invention: Nucleoside phosphoramidate prodrugs

We, as the third party, are a non-profit organization called I-MAK based in U.S.A. For years we have been dedicated to helping low-income people, especially those in developing countries, be able to afford expensive medicaments for their diseases, by invalidating undeserved medicine patents or preventing undeserved medicine patent applications from being approved.

Many people in developing countries are unable to pay for overpriced medicaments and have long been suffering from adverse conditions for lack of effective treatment. One of these overpriced medicaments is Sofosbuvir (Sovaldi), which is a highly effective anti-HCV (Hepatitis C virus) drug. One PCT application related to Sofosbuvir, PCT/US2008/058183, has entered the national phase of China and is
under examination, and its application number in China is 200880018024.2. Here, we believe this patent application is non-patentable in the sense of the Chinese Patent Law and therefore provide the following 3rd-party observations.

As several amendments to the application documents of this application have been filed in China so far, we do not know its current claims. Therefore, our observations below are based on the claims of this PCT application in the national phase of India (see Appendix 1: India claims and a Chinese translation thereof). We politely request the Examiner to consider our observations in the examination of the corresponding claims/technical solutions in the current claim set. We are truly grateful for this.

In the observations, we cite the publications listed below and attach a copy for each of them, which are all documents in the prior art to the target application.

**D1**: CN1816558A (published on August 9, 2006)


**D3**: WO 2005/012327 A2 (published on Feb 10, 2005)


The Examiner may use any combination of the above documents when necessary, in a manner not limited to those present in the following observations.

With regard to the claims of Appendix 1, we believe that,
- claims 1-14 do not have an inventive step, which does not conform to the provisions of Article 22, paragraph 3 of the Chinese Patent Law;
- claims 4-5 and 11-12 claim non-patentable subject matters, which does not conform to the provisions of Article 25, paragraph 1, item (3) of the Chinese Patent Law;
- claims 8-12 claim technical solutions that are not sufficiently disclosed in the Description, which does not conform to the provisions of Article 26, paragraph 3 of the Chinese Patent Law; and
- claims 1-5 are not supported by the Description, which does not conform to the provisions of Article 26, paragraph 4 of the Chinese Patent Law,
detailed reasons for which are stated in following pages.

Throughout the observations, expressions like “in the art” mean the prior art to the target application.
I. Common knowledge and conventional technical means in the art related to the target application

1. Use of nucleoside analogs as antiviral agents and its working mechanism

As well known to persons skilled in the art, viruses replicate their genetic materials in their host cell basically through the following mechanism: RNA viruses and reverse-transcribing (RT) viruses rely on their special DNA/RNA polymerase to synthesize viral DNA/RNA chains in the host cell, while DNA viruses use host DNA polymerases to synthesize their viral DNA chains. The basic building blocks that DNA/RNA polymerases recognize and use to synthesize viral DNA/RNA are 5’-triphosphate nucleosides (NTP, where N=A, U/T, G, C). Nucleoside (N), after entering the cell, is converted into its 5’-monophosphate (NMP) by the intracellular host or viral nucleoside kinase, NMP is further converted into the 5’-triphosphate form (NTP), and then NTP is recognized by host or viral RNA/DNA polymerases and added to the tail of the viral DNA/RNA chain being synthesized (see for example the following figure for RNA).
Based on this mechanism, people in the art have long been using nucleoside analogs (N’) able to be recognized by viral DNA/RNA polymerases or viral nucleoside kinases to eventually inhibit the chain extension of viral DNA/RNA. Specifically, such nucleoside analogs (N’) are recognized by host or viral nucleoside kinases and converted sequentially into their 5’-triphosphate (N’TP), and N’TP is then recognized by a corresponding host or viral DNA/RNA polymerase in the cell so as to compete with natural 5’-triphosphate nucleosides (NTP), and finally added to the tail of the viral DNA/RNA chain being synthesized. The extension of the viral DNA/RNA chain is terminated because of the difference between the analog and natural nucleosides, which results in suppression of viral replication.

The earliest antiviral nucleoside analog that went commercial could be traced back to an anti-herpes virus uridine analog called Idoxuridine (Prusoff WH, (1959) Synthesis and biological activities of iododeoxyuridine, an analog of thymidine, *Biochim Biophys Acta*. 32(1):295-6). Since then many nucleoside analogs have been discovered and applied as inhibitors of viral enzymes involved in viral DNA/RNA synthesis, for example but not limited to, those listed in Table 1 below.

Table 1. Anti-viral nucleoside analogs known in the prior art

<table>
<thead>
<tr>
<th>Name of nucleoside analog (anti-viral drugs (other names) [Reference])</th>
<th>Target for inhibition</th>
<th>Analogous to</th>
<th>Publication time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-β-D-arabinofuranosyladenine (Vidarabine)</td>
<td>DNA polymerase of multiple viruses</td>
<td>adenosine</td>
<td>1964</td>
</tr>
<tr>
<td>Acycloguanosine(ACV, Aciclovir)</td>
<td>herpes simplex virus thymidine kinase; varicella herpes zoster virus thymidine kinase</td>
<td>guanosine</td>
<td>1970s</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Hepatitis C virus (HCV) RNA polymerase</td>
<td>guanosine/adenosine</td>
<td>1972</td>
</tr>
</tbody>
</table>

1 See for example:
- Wagner 2000, the last paragraph on page 417, where use of nucleoside analogs for inhibition of various viruses is described.
- D1, item “10)” on pages 11-13, which describes research and results about use of various nucleoside analogs for treatment of Flaviviridae infections from 1994 to 2004.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Enzyme Activity</th>
<th>Inhibitory Base</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2′,3′-dideoxy-3′-thiacytidine (3TC, Lamivudine)</td>
<td>Hepatitis B virus (HBV) reverse transcriptase; HIV reverse transcriptase</td>
<td>cytidine</td>
<td>1980s</td>
</tr>
<tr>
<td>Stavudin (d4T)</td>
<td>HIV reverse transcriptase</td>
<td>thymidine</td>
<td>1980s</td>
</tr>
<tr>
<td>Azidothymidine (AZT, Zidovudine)</td>
<td>HTLV-III/LAV reverse transcriptase</td>
<td>thymidine</td>
<td>1985</td>
</tr>
<tr>
<td>2′,3′-dideoxyinosine (ddI, Didanosine)</td>
<td>HIV reverse transcriptase</td>
<td>adenosine</td>
<td>1988</td>
</tr>
<tr>
<td>2′,3′-dideoxycytidine (ddC, Zalcitabine)</td>
<td>HIV reverse transcriptase</td>
<td>cytidine</td>
<td>1988</td>
</tr>
<tr>
<td>dideoxy uridine (ddU) 5′-phosphates [R2]</td>
<td>HIV reverse transcriptase</td>
<td>uridine</td>
<td>1994</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>HIV reverse transcriptase</td>
<td>cytidine</td>
<td>1996</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>HIV reverse transcriptase</td>
<td>guanosine</td>
<td>Before 1998</td>
</tr>
<tr>
<td>DHPG (Ganciclovir)</td>
<td>Cytomegalovirus guanosine kinase</td>
<td>guanosine</td>
<td>1998</td>
</tr>
<tr>
<td>Entecavir (ETV)</td>
<td>HBV reverse transcriptase</td>
<td>guanosine</td>
<td>1990s</td>
</tr>
<tr>
<td>(2′R)-2′-dO-2′-F-2′-C-methyluridine 5′-phosphate [WO2005003147 A2]</td>
<td>HCV RNA polymerase</td>
<td>uridine</td>
<td>2005</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>HBV reverse transcriptase</td>
<td>thymidine</td>
<td>2005</td>
</tr>
<tr>
<td>4′-azido-uridine 5′-phosphoramidate [WO2007020193A2]</td>
<td>HCV RNA polymerase</td>
<td>uridine</td>
<td>2007.2</td>
</tr>
</tbody>
</table>

As can be seen clearly, until February 2007, it has been a conventional technical means in the art to use nucleoside analogs to suppress viral replication by incorporating its 5′-triphosphate into viral DNA/RNA chains.

2. **Monophosphorylation of a nucleoside analog is generally the rate-limiting step in the course to its triphosphate, and suitable 5′-phosphate prodrugs of a nucleoside analog accelerate its cross-membrane delivery into cells and intracellular triphosphorylation.**
It is well known that, for incorporation of a nucleoside analog into the viral DNA/RNA chain, kinase-mediated 5’-monophosphorylation of the nucleoside analog (N’→N’MP) is generally the rate-limiting step in the course of its triphosphorylation\(^2\).

Although 5’-triphosphate of some nucleoside analogs (N’TP) are potent viral inhibitors, these nucleoside analogs (N’) themselves show low or no activity in inhibition tests, generally because of the host cell’s lack of corresponding kinase activity which renders the 5’-monophosphorylation of these analogs extremely slow\(^3\).

In order to address this issue, it was contemplated in the art to use the 5’-phosphate of nucleoside analogs as a prodrug to “bypass” the kinase-mediated monophosphorylation so that it can be quickly converted into the active triphosphate form. Since the unmodified 5’-monophosphate of a nucleoside or its analogs (NMP)

\(^2\) See for example:
- Wagner 2000, line 8 on page 418 reads that ddNs’ activation is hindered at the first phosphorylation step.
- McGuigan 2006, lines 13-15 of the 1st paragraph in the left column on page 7215 and its citation (3): in most cases the first phosphorylation to the 5’-monophosphate is the rate-limiting step;
- D2 (Perrone 2007), lines 2-5 of the 3rd paragraph in the right column on page 1840: the first phosphorylation step to produce the 5’-monophosphate has often been found to be the rate-limiting step in the pathway to intracellular nucleotide triphosphate formation.

\(^3\) See for example:
- McGuigan 1994, the 1st paragraph in the left column on page 11: nucleoside analogs have limitations because they depend on kinase-mediated activation to generate the bio-active (tri)phosphate forms; and the 2nd last line in the left column to line 4 in the right column on page 11: dideoxythymidine and 3’-O-methylthymidine are nucleoside analogs which are inactive against HIV, while their triphosphates are exceptionally potent inhibitors of HIV reverse transcriptase; the inactivity of these nucleoside analogs is attributed to poor phosphorylation by host cells.
- McGuigan 1996, lines 13-24 in the left column on page 1748: in many cases ddN derivatives have a poor affinity for nucleoside kinases; dependence on phosphorylation for activation of the particular nucleoside analog may be a particular problem in cells where the nucleoside kinase activity is low or even lacking.
- McGuigan 2006, lines 6-10 of the 1st paragraph in the left column on page 7215: poor phosphorylation can be a major cause of poor activity, with several examples now known where nucleoside analogs are inactive but the corresponding triphosphates are inhibitors at their enzyme target.
The 3rd-party observations against CN 200880018024.2

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has a poor cell-membrane-permeation ability and relatively poor stability in the physiological environment, in as early as 1960 it was proposed that the phosphate group therein be modified to promote permeation of phosphate-based esters of nucleoside analogs and to increase their intracellular availability. Since 1990 or earlier, stable 5’-phosphate-based prodrugs of nucleoside analogs have been designed and employed to improve the intracellular delivery and activation of the nucleoside analogs, and such prodrugs can be readily hydrolyzed into 5’-monophosphate of the nucleoside analogs (N’MP) by related enzymes inside the cell, which is then rapidly converted into the triphosphate form to be fully activated. Such a technique has been called “Pronucleotide” or simply “ProTide” 4.

This “ProTide” technology in the prior art have shown great success in the intracellular delivery and activation of many nucleoside analogs. By modification of

4 See for example:
- McGuigan 1994, the Abstract and lines 5-18 in the right column on page 11: certain phosphate triester derivatives of the inactive nucleoside analog dideoxy uridine (ddU) are inhibitors of HIV replication at µM levels, and they successfully bypass the nucleoside kinase; this “kinase bypass strategy” has been successful for several other highly modified nucleoside analogs.
- Wagner 200, lines 3-7 of the 2nd paragraph on page 419 and its citation (8): various prodrug or “pronucleotide” approaches have been devised and investigated, with the general goal of promoting passive diffusion through cell membranes and increasing the bio-availability of phosphorylated nucleosides; this approach of derivatization has been applied using various protecting groups for the phosphate moiety.
- Cahard 2004, the Abstract and the first paragraph in the left column on page 374: aryloxy phosphoramidate triesters are an effective pro-tide motif for the intracellular delivery of charged antiviral nucleoside monophosphates; the phenyl alanyl phosphoramidate approach is conformed to be successful on a range of nucleosides by many research groups.
- McGuigan 2006, the 8th last line to the 5th last line in the left column on page 7215 and its citations (4)-(6): in order to bypass the nucleoside kinase dependence of nucleoside analogs, many groups have worked on phosphate prodrug (“ProTide”) strategies.
- D2 (Perrone 2007), the last 4 lines of the 3rd paragraph in the right column on page 1840: unmodified nucleoside monophosphates are unstable in biological media and also show poor membrane permeation because of the associated negative charges at physiological pH; lines 1-7 of the 4th paragraph in the right column on page 1840: our aryloxy phosphoramidate ProTide approach allows bypass of the initial kinase dependence by intracellular delivery of the mono-phosphorylated nucleoside analog as a membrane permeable ProTide form. This technology greatly increases the lipophilicity of the nucleoside monophosphate analog with a consequent increase of membrane permeation and intracellular availability.
the phosphate group at the 5'-position of nucleoside analogs of interest, a large number of thus-modified 5'-phosphate of nucleoside analogs have shown a boost in the inhibition activity on virus replication by tens, hundreds, or even thousands of times, in comparison with the parental nucleoside analogs.

Therefore, the “Pronucleotide” or “ProTide” strategy, i.e. use of 5'-phosphate-based prodrugs to promote the intracellular delivery and triphosphorylation of nucleoside analogs and eventually to boost their antiviral activity, has been a conventional technical means in the art.

In summary, for antiviral 5'-phosphate-based prodrugs of a nucleoside analog, their ultimate antiviral activity lies in the nucleoside analog itself, which terminates the viral DNA/RNA chain extension by its structural difference from natural nucleosides; their intracellular delivery (cell membrane permeation) relies on the lipophilicity rendered by the modified phosphate group; and their intracellular hydrolysis into the monophosphate form is mainly attributed to the structural nature of the modified phosphate group and the corresponding enzymes in the host cell.

3. The target application has its inventions made based on the above common knowledge and conventional technical means in the art.

In the “Background Art” section of the Description of the target application, paragraphs [0017], [0018], and [0019] (see below, especially the underlined text), as well as the prior-art documents cited therein, explicitly recite the antiviral principle of

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5 See for example:
- McGuigan 1994, Figure 1 and lines 12-14 of the 2nd paragraph in the right column on page 13: the aryloxy phosphoramidate (3c) of a ddU increases its potency by approximately 50 times.
- Cahard 2004, Figure 1 and the 2nd paragraph in the right column on page 374: the aryloxy phosphoramidate prodrug (21) for d4A boosts the activity of the parental nucleoside analog d4A by 1000-4000 fold; the aryloxy phosphoramidate prodrug (22) for ddA boosts the activity of the parental nucleoside analog ddA by >100 fold.
- McGuigan 2006, the Abstract: the ProTide approach is highly successful when applied to L-Cd4A with potency improvements in vitro as high as 9000-fold against HIV; Table 1 also shows that several aryloxy phosphoramidate prodrugs achieve an anti-HIV activity at the level of about 10 nM.
nucleoside analogs and the use of 5’-phosphate-based prodrugs of nucleoside analogs
to bypass the rate-limiting mono-phosphorylation and promote intracellular delivery.
In particular, paragraph [0019] mentions “pronucleotides”, which is exactly the
conventional technical means described above that has been studied and embodied
over the last 20 years. It can be clearly seen that the target application makes its
inventions by selecting specific nucleoside analogs and modified 5’-phosphate groups
right based on the common knowledge and conventional technical means “ProTide”
in the prior art.

Paragraphs [0017]-[0019] of the target application (from CN 101918425 A):

“[0017] Nucleoside inhibitors of NS5B polymerase can act either as a non-natural
substrate that results in chain termination or as a competitive inhibitor which
competes with nucleotide binding to the polymerase. To function as a chain
terminator the nucleoside analog must be taken up by the cell and converted in vivo to
a triphosphate to compete for the polymerase nucleotide binding site. This conversion
to the triphosphate is commonly mediated by cellular kinases which imparts
additional structural requirements on a potential nucleoside polymerase inhibitor.
Unfortunately, this limits the direct evaluation of nucleosides as inhibitors of HCV
replication to cell-based assays capable of in situ phosphorylation.”

“[0018] In some cases, the biological activity of a nucleoside is hampered by its poor
substrate characteristics for one or more of the kinases needed to convert it to the
active triphosphate form. Formation of the monophosphate by a nucleoside kinase is
generally viewed as the rate limiting step of the three phosphorylation events. To
circumvent the need for the initial phosphorylation step in the metabolism of a
nucleoside to the active triphosphate analog, the preparation of stable phosphate
prodrugs has been reported. Nucleoside phosphoramidate prodrugs have been shown
to be precursors of the active nucleoside triphosphate and to inhibit viral replication
when administered to viral infected whole cells (McGuigan, C, et al., J. Med. Chem.,
Agents and Chemotherapy, 2005, 49, 1898); US 2006/0241064; and WO 2007/095269.”

“[0019] Also limiting the utility of nucleosides as viable therapeutic agents is their sometimes poor physicochemical and pharmacokinetic properties. These poor properties can limit the intestinal absorption of an agent and limit uptake into the target tissue or cell. To improve on their properties prodrugs of nucleosides have been employed. It has been demonstrated that preparation of nucleoside phosphoramidates improves the systemic absorption of a nucleoside and furthermore, the phosphoramidate moiety of these "pronucleotides" is masked with neutral lipophilic groups to obtain a suitable partition coefficient to optimize uptake and transport into the cell dramatically enhancing the intracellular concentration of the nucleoside monophosphate analog relative to administering the parent nucleoside alone. Enzyme-mediated hydrolysis of the phosphate ester moiety produces a nucleoside monophosphate wherein the rate limiting initial phosphorylation is unnecessary.”
II. Claim 1 of the target application does not possess an inventive step as demanded under Article 22, paragraph 3 of the Chinese Patent Law

Claim 1 seeks to protect a compound, which is used to treat Hepatitis C virus (HCV) as explained in the Description. Specifically, claim 1 seeks to protect “(S)-2-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]phosphorylamino]-propionic acid isopropyl ester” or a stereoisomer thereof. As can be seen, the quoted compound is Sofosbuvir, represented by the following structural formula.

![Sofosbuvir Structural Formula](image)

It is clear that this compound is a 5’-phosphate prodrug of the uridine analog “(2’R)-2’-deoxy-2’-fluoro-2’-C-methyluridine”, wherein the 5’-phosphate group is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group.

We believe above claim 1 lacks an inventive step over D1 and D2 in combination with the common knowledge and conventional technical means in the art, the reasons for which are stated below.

1. D1 (CN1816558A, published in Chinese on August 9, 2006; its PCT publication is WO 2005/003147, published on January 13, 2005) discloses a set of nucleoside analogs or their prodrugs as HCV inhibitors, and the core structure of these analogs is 2’-deoxy-2’-fluoro-2’-C-methyl nucleoside and its 5’-modified prodrugs. Specifically, D1 discloses an HCV RNA polymerase inhibitor and its use in treating HCV in for example claim 40:

   “Claim 40. Use of an anti-virally effective amount of a (2’R)-2’-deoxy-2’-fluoro- 2’-C-methyl nucleoside (β-D or β-L) of the
following formula or its pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier, for the treatment or prophylaxis of hepatitis C infection in a host:

\[
\begin{align*}
\text{Base} & \quad \text{R}^1 \quad \text{R}^7 \\
\end{align*}
\]

wherein Base is

\[
\begin{align*}
\text{R}^1 \quad \text{R}^7 \\
\end{align*}
\]

It can be seen that, when \( \text{R}^3 = \text{H} \) and \( \text{R}^4 = \text{OH} \), the base is uridine. In this case, when \( \text{R}^1 = \text{phosphate} \) and \( \text{R}^7 = \text{H} \), the compound is a 5'-phosphate of “(2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine”, which has exactly the same nucleoside moiety as the compound of claim 1 of the target application (Sofosbuvir). That is to say, D1 discloses that a 5'-phosphate of “(2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine” is an HCV inhibitor.

Furthermore, Example 5 of D1 experimentally validates the HCV inhibition effect of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl cytidine (see the formula below), which proves
that the 5’-triphosphate of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl cytidine (i.e. C’TP) (which is an example compound of Claim 40, where R\(^1\)=triphosphate, R\(^7\)=H, R\(^3\)=H, and R\(^4\)=NH\(_2\)) is an active and potent HCV inhibitor. Since D1 discloses that the Base can be a purine or pyrimidine and also defines that pyrimidine includes uracil, and, more importantly, it is common knowledge that uracil is one of the four bases in RNA, a person skilled in the art would be fully able to infer that replacing the cytidine in the active (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl cytidine 5’-triphosphate (C’TP) with a uridine (R\(^4\)=OH) will give a likewise active and potent HCV inhibitor (U’TP). Therefore, D1 not only discloses that 5’-phosphates of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine are HCV inhibitors, but also teaches a person skilled in the art to choose it as an active agent. In other words, based on the experimental results of Example 5 of D1 and the common knowledge in the art, a person skilled in the art will be fully motivated to specifically choose, from the various compounds encompassed by Claim 40, the 5’-phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug, as defined in claim 40) of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine as a practicable HCV inhibitor.

Moreover, Claim 40 of D1 also defines that the 5’-phosphate can be a “stabilized phosphate prodrug” which when administered in vivo is capable of providing a compound wherein R\(^1\) or R\(^7\) is independently H or phosphate. This definition indicates that the 5’-phosphate can be further modified in order to stabilize the prodrug, and the stabilized phosphate prodrug will turn into the 5’-monophosphate form (R\(^1\)=phosphate, and R\(^7\)=H) to be activated. And the 3\(^{rd}\) paragraph on page 46 of D1 reads that “Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known.
In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1, 2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 27 (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.”; the 3rd paragraph on page 57 of D1 also reads “The nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono-, di- or triphosphate of the nucleoside reduces polarity and allows passage into cells. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, Antiviral Research, 1995, 27: 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.”

Therefore, D1 explicitly discloses and teaches that alkylation, acylation, arylation, or other lipophilic modification can be made to the phosphate group in the 5’-phosphate of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine to increase its activity, bioavailability and stability, and the modified prodrug will be converted into the 5’-monophosphate form (U’MP) after its entry into the cell.

In addition, with reference to the common knowledge and conventional technical means in the art as described in Part I, a person skilled in the art will also be fully motivated to use the ProTide strategy to select a suitable stable 5’-phosphate group for (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine, in order to increase its activity, bioavailability and stability.

Hence, claim 1 of the target application is different from the above contents disclosed in D1 merely in that the stable 5’-phosphate group on the nucleoside analog in claim 1 is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group. Then the technical problem that claim 1 aims to solve is: which modified 5’-phosphate group to select to increase
the activity, bioavailability and stability of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine 5’-phosphate and allow the prodrug to be converted into an active 5’-monophosphate form (U’MP) after it enters the cell.

2. D2 (Perrone 2007) discloses that use of an aryloxy phosphoramidate group as the 5’-group of a uridine analog can significantly boost the inhibitory activity against the HCV RNA polymerase. Specifically, D2 discloses that the nucleoside analog 4’-azido-cytidine is a potent HCV inhibitor, but 4’-azido-uridine (AZU) (see its structure below) does not show inhibitory activity in the inhibition assay against RNA replication of HCV (see the last paragraph in the left column to the 2nd paragraph in the right column on page 1840 of D2). The reason is presumed to be the extremely slow intracellular 5’-monophosphorylation of AZU (see the 3rd paragraph in the right column on page 1840 of D2).

![AZU Structure](image)

To address this issue, D2 employs the conventional ProTide strategy in the art and prepares about 20 stable phosphate-based prodrugs of AZU (see the structure below), wherein the aryl group on the phosphate group renders the prodrugs strong lipophilicity so that the prodrugs can easily permeate the cell membrane. These prodrugs are hydrolyzed into 5’-monophosphorylated AZU in the cell to bypass the kinase-mediated monophosphorylation (see the 4th paragraph in the right column on page 1840 to the 1st paragraph in the left column on page 1841).

![Aryloxy phosphoramidate prodrugs of AZU](image)
Among these aryloxy phosphoramidate prodrugs, D2 particularly points out that “the isopropyl ester (15) showed high potency and represented one of the most active phosphoramidates prepared” (see the 4th and 5th last lines in the right column on page 1842 of D2). In addition, prodrug No.15 shows an EC$_{50}$=0.77 µM, at least 100 times more than the EC$_{50}$ (>100 µM) of unmodified AZU. In prodrug No.15, R=methyl (to form L-alanine) and R’=isopropyl (see Table 1 on page 1843 of D2). That is, the stable 5’-phosphate group in prodrug No.15 of D2 is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group, i.e. exactly the 5’-phosphate group in claim 1 of the target application.

It can be seen that, D2 discloses that a stable modified 5’-phosphate group suitable for nucleoside analog 5’-phosphates is the “(phenyl)(isopropyl-L-alaninyl)phosphate” group, which has the same function in D2 as in D1, i.e., a function of increasing the activity, bioavailability and stability of an anti-HCV uridine analog, with the same mechanism and purpose of promoting intracellular delivery of a uridine analog and bypassing the kinase-mediated 5’-monophosphorylation.

Therefore, after reading D1 and D2, in order to obtain a more active prodrug, a person skilled in the art would have easily envisaged applying the aryloxy phosphoramidate group identified to be highly active in D2 to the phosphate group in the (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine 5’-phosphate disclosed and taught in D1. Since AZU and (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine are both uridine analogs used to inhibit HCV through the same inhibition mechanism (i.e., turning into their 5’-triphosphate form and mimicking natural uridine to incorporate themselves into viral RNA chain and terminate the chain extension), in conjunction with the common knowledge and conventional technical means in the art as described in Part I, the structural difference between these two uridine analogs themselves will not prevent a person skilled in the art, who tries to obtain a more active and potent prodrug of a nucleoside analog by improving its intracellular delivery and bypassing its kinase-mediated monophosphorylation, from applying AZU’s modified 5’-phosphate group to the 5’-position of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine.

In addition, there are only 6 highly active aryloxy phosphoramidate groups
particularly nominated in D2 (i.e. No.14, 15, 17, and 33-35). A person skilled in the art can try them all to attach each of them to the 5’-position of (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine to obtain the compound of claim 1 of the target application, which does not need any creative work.

In conclusion, it is obvious for a person skilled in the art to obtain the technical solution of claim 1 of the target application based on D1 and D2 in combination of the common knowledge in the art. Claim 1 of the target application does not have any prominent substantive features or notable progress over D1 and D2, and therefore does not have an inventive step.

3. Claim 1 of the target application does not produce any unexpected effects

Firstly, D2 has provided the technical teaching that use of the “(phenyl)(isopropyl-L-alaninyl)phosphate” group (No.15) as the 5’-phosphate group of a uridine analog can significantly boost the activity of anti-HCV nucleoside analogs. Therefore, since D2 and the target application employ the same mechanism and theory, the activity improvement achieved in the target application using the same modified 5’-phosphate group is expectable to a person skilled in the art.

Furthermore, the “(phenyl)(isopropyl-L-alaninyl)phosphate” group (No.15) disclosed in D2 boosts the inactive parent nucleotide analog AZU (EC₅₀ >100 µM) to an activity of EC₅₀ = 0.77 µM, while the target application uses the same phosphate group to boost the parent (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine to an activity of EC₉₀ = 0.39 µM, which is of the same magnitude of that achieved in D2. Therefore, even if (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine is inactive like AZU, the target application does not produce an effect beyond the expectation of a person skilled in the art.

Thirdly, in the prior art, use of phosphoramidate prodrugs (ProTide) has achieved increases in antiviral activity of as high as thousands of times the activity of the unmodified parent nucleoside analog, even to an activity of several nM (see for example McGuigan 2006, the Abstract and Table 1). With regard to HCV specifically, use of phosphoramidate prodrugs (ProTide) has achieved an increase in anti-HCV
activity of more than 450 times as compared to the inactive unmodified parent uridine analog, to an activity of EC$_{50}$=0.22 µM (see lines 7-10 of the last paragraph in the right column on page 1843 of D2 and Table 3 of D2). In comparison, the target application employs the conventional ProTide technology and the particular group “(phenyl)(isopropyl-L-alaninyl)phosphate” that has been identified in the art as a highly active group to boost the activity of a known nucleoside analog to EC$_{90}$=0.39 µM, which is completely within the expectation of a person skilled in the art.

In conclusion, claim 1 of the target application does not have an inventive step, and does not conform to the provisions of Article 22, paragraph 3 of the Chinese Patent Law.

III. Claims 2 and 3 of the target application do not have an inventive step, which does not conform to the provisions of Article 22, paragraph 3 of the Chinese Patent Law.

Claims 2 and 3 each seek to protect a composition comprising the compound of claim 1. Pharmaceutically acceptable media are conventional media used in the art for preparation of compositions. Therefore, since claim 1 does not have an inventive step, claims 2 and 3 also do not have an inventive step.

IV. Claims 4 and 5 of the target application are treatment methods for diseases, which do not conform to the provisions of Article 25, paragraph 1, item (3) of the Chinese Patent Law.

Claims 4 and 5 each claim a method of using the compound of claim 1 to treat virus infections or HCV infections in a subject. Both claims are methods for treating diseases of a human or animal as provided in Article 25, paragraph 1, item (3) of the Chinese Patent Law, and hence cannot be patented.

Even if the applicant rewrites claims 4 and 5 into claims of use of the compound in manufacture of medicaments, they will still lack an inventive step, for above the
reasons in the comments on claim 1.

V. Claims 6 and 7 of the target application do not have an inventive step, which does not conform to the provisions of Article 22, paragraph 3 of the Chinese Patent Law.

Claim 6 of the target application claims a process for preparing the compound or a stereoisomer thereof as claimed in claim 1, said process comprising reacting a compound 4” with a nucleoside analog 5’:

![Chemical structure](image1)

wherein X’ is a leaving group.

D3 (WO 2005012327 A2) discloses a compound and the preparation method thereof. Page 3 of the Description of D3 specifically discloses a compound of formula (I) or a pharmaceutically acceptable derivative or metabolite thereof:

![Chemical structure](image2)
wherein:
R is selected from the group comprising alkyl, aryl and alkylaryl;
R' and R" are, independently, selected from the group comprising H, alkyl and alkylaryl, or R' and R" together form an alkylene chain so as to provide, together with the C atom to which they are attached, a cyclic system;
Q is selected from the group comprising -O- and -CH₂-;
X and Y are independently selected from the group comprising H, F, Cl, Br, I, OH and methyl (-CH₃);
Ar is a monocyclic aromatic ring moiety or a fused bicyclic aromatic ring moiety, either of which ring moieties is carbocyclic or heterocyclic and is optionally substituted;
Z is selected from the group comprising H, alkyl and halogen; and
n is 0 or 1, wherein when n is 0, Z' is -NH₂ and a double bond exists between position 3 and position 4, and when n is 1, Z' is =O;
with the proviso that when n is 1, X and Y are both H, R is methyl (-CH₃), one of R' and R" is H and one of R' and R" is methyl (-CH₃), then Ar is not phenyl (-C₆H₅).

Line 20 on page 7 of the Description of D3 also discloses “Preferably, R is methyl, ethyl, n- or i- propyl”.

Lines 5-6 on page 8 discloses “preferred compounds include those where R' and R" are both methyl, one of R' and R" is H and one of R' and R" is methyl, and…”.

Line 14 on page 9 discloses “preferably Q is O”.

Lines 1-2 on page 11 discloses “More preferably, Ar is selected from the group comprising: Ph- …”.

The last paragraph on page 16 to line 5 on page 17 further discloses a process for the preparation of a compound having formula (I) above, the process comprising reacting of a compound of formula (III) with a compound of formula (IV):
wherein, Ar, n, Q, R, R', R'', X, Y, Z and Z' have the meanings described above with respect to formula (I).

Therefore, when Q=O, n=1, Z'=O, Z=H, X=-CH$_3$, Y=F, Ar=phenyl, R=isopropyl, R'=H, and R''=-CH$_3$, the compound of formula (I) of D3 will be identical to the compound of claim 1 of the target application. In this case, in the process disclosed on pages 16-17 of D3, the compound of formula (III) is identical to the nucleoside analog 5’ of claim 6 of the target application, and the compound of formula (IV) is identical to the compound 4’’ of claim 6 of the target application except the Cl bonded to the phosphorous atom, while Cl is an example of a leaving group (X’). Therefore, D3 discloses a general synthesis method covering the method of claim 6, in which a phosphate-based prodrug of nucleoside analogs is synthesized from (i) an arylxy phosphoramidate with a leaving group Cl and (ii) a uridine analog. When facing the technical problem of how to synthesize the compound of claim 1 of the target application (i.e. Sofosbuvir), a person skilled in the art under the teaching of D3 would have readily envisaged using the phosphate moiety of Sofosbuvir (i.e. the (phenyl)(isopropyl-L-alaninyl)phosphate) having a leaving group (e.g. Cl) to react with the nucleoside analog moiety of Sofosbuvir (i.e. (2’R)-2’-deoxy-2’-fluoro-2’-C-methyl uridine) to obtain the target compound. That is, the process of claim 6 of the target application would have been easily envisaged by a person skilled in the art under the teaching of the process of D3. In addition, the process of claim 6 of the target application does not produce any unexpected technical effects. Hence, the process of claim 6 of the target application does not have an inventive step over D3.

Claim 7 of the target application seeks to protect a product comprising the compound or a stereoisomer thereof as claimed in claim 1 obtained by a process comprising
reacting a compound 4” with a nucleoside analog 5’ (e.g. the process of claim 6). As commented above, since neither the compound of claim 1 nor the process of claim 6 has an inventive step, claim 7 does not have an inventive step.

VI. Claims 8-12 claim technical solutions that are not sufficiently disclosed in the Description, which does not conform to the provisions of Article 26, paragraph 3 of the Chinese Patent Law.

Claim 8 of the target application seeks to protect the (S)-phosphate isomer of the compound of claim 1. However, the Description of the target application only experimentally validates a mixture of diastereoisomers of “(S)-2-[(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]phenoxy-phosphorylamino]-propionic acid isopropyl ester”, without validating its specific (R)- or (S)- isomer with respect to the phosphate group. Which diastereoisomer is responsible or mainly responsible for the overall activity is unpredictable and needs experiments to verify. Therefore, a person skilled in the art will be unable to know beforehand that the (S)-phosphate isomer of claim 8 has a considerable activity.

Furthermore, Example 81 of the target application also discloses that one diastereoisomer of each of Examples 15, 39 and 49 shows lower activity than the corresponding diastereoisomeric mixture. Therefore, a person skilled in the art has reason to believe that not all diastereoisomers can solve the technical problem that the target application aims to solve and can produce the same technical effects.

Hence, claim 8, as well as claims 9-12, is not disclosed in a sufficient manner, which does not conform to the provisions of Article 26, paragraph 3 of the Chinese Patent Law.

In addition, claims 11-12 are methods for treatment of diseases and thus are non-patentable in the sense of Article 25.1.(3) of the Chinese Patent Law.
VII. Claims 13 and 14 of the target application do not have an inventive step, which does not conform to the provisions of Article 22, paragraph 3 of the Chinese Patent Law.

Claims 13 and 14 do not have an inventive step, for the same reasons commented on claims 6 and 7.

VIII. Claims 1-5 are not supported by the Description, which does not conform to the provisions of Article 26, paragraph 4 of the Chinese Patent Law.

Claims 1-5 all involve technical solutions of “stereoisomers”. However, the Description of the target application only experimentally validates a mixture of diastereoisomers of “(S)-2-\{(2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydrofuran-2-ylmethoxy]phenoxy-phosphorylamino\}-propionic acid isopropyl ester”, without validating its specific isomers. Which diastereoisomer is responsible or mainly responsible for the overall activity is unpredictable and needs experiments to verify. Therefore, a person skilled in the art has reason to doubt that all the stereoisomers have a considerable activity.

Furthermore, Example 81 of the target application also discloses that one diastereoisomer shows lower activity than the corresponding diastereoisomeric mixture. Therefore, a person skilled in the art has reason to believe that not all diastereoisomers can solve the technical problem that the target application aims to solve and can produce the same technical effects.

Therefore, the technical solutions involving “stereoisomers” in claims 1-5 are not supported by the Description, which does not conform to the provisions of Article 26, paragraph 4 of the Chinese Patent Law.

IX. Conclusion
In conclusion, none of claims 1-14 of the target application meets the requirements for patentability as provided in the Chinese Patent Law. Therefore, we believe the claims of the target application do not conform to the relevant provisions of the Chinese Patent Law and should not be granted with a patent right. We sincerely request the Examiner to consider our observations in examination of the target application. Thanks!

Yours faithfully
The third Party
I-MAK
26 September 2014