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May 23, 2015

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The Controller of Patents
Intellectual Property Office Building,
CP-2, Sector V, Salt Lake City,
Kolkata-700091
Phone: 033-23679101

Ref: Patent Application No. IN 3658/KOLNP/2009 of Pharmasset Inc
Sub: Pre-Grant Represention/Opposition to the Patent Application u/s 25 (1) of the Patents Act, 1970 and Rules 55(1) of the Patent Rules, 2003.
Representation filed by: Virupaksha Organics Limited
Our Ref: SOFOVIR- A2320

Dear Sir,

We are filing this pre-Grant representation/Opposition u/s 25 (1) of the Patents Act, 1970 and Rules 55(1) of the Patent Rules, 2003 in Form 7A. In this connection, we are enclosing herewith the following documents in duplicate for your consideration.

1. Form 7A
2. Index to the list of documents
3. Written statement of representation
4. Documents in support of written statement.

We request to take the above documents on record.

Under Section 25 (1) of the Patents Act, 1970 and Rules 55(1) of the Patent Rules, 2003, we request an opportunity to be heard in the above matter and to be kept informed of any reply to the said representation by the patent Applicant.

Yours sincerely,

Dr. S. Padmaja
iProPAT Intellectual Property Solutions

Encl: As above

VS/Patent Office Cover Letter 23052015

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Document 2: WO 2005/012327 A2 assigned to Univ Cardiff; published on February 10, 2005	957-1080
Document 3: Jeremy L. Clark; Journal of Medicinal Chemistry 2005, Vol 48, 5504-5508; published by Pharmasset Ltd on Jul 26, 2005	1081-1085
Document 4: Plinio Perrone; Journal of Medicinal Chemistry 50, 1840-1849, 2007 published by Cardiff University on Mar 17, 2007	1086-1095
Document 5: WO 2001/092282 A2 assigned to Idenix published on December 6, 2001	1096-1397
D6: Cahard, Dominique; Mini-Reviews in Medicinal Chemistry, 2004, 4, 371-381 published by Cardiff University on May 1, 2004	1398-1409
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D8: FEBS Letters 1994, 351, 11-14, published by Cardiff University	1419-1423
D9: Antiviral Research 35, 195-204, 1997, published by Cardiff University	1424-1433

BEFORE THE CONTROLLER OF PATENTS – KOLKATA

IN THE MATTER OF SECTION 25(1) OF THE PATENTS ACT, 1970 AS AMENDED BY THE PATENTS (AMENDMENT) ACT 2005

And

IN THE MATTER OF THE PATENTS RULES, 2003 AS AMENDED BY THE PATENTS (AMENDMENT) RULES 2006

And

IN THE MATTER OF THE PATENT APPLICATION No. 3658/KOLNP/2009 DATED October 20, 2009 TITLED "NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS" IN THE NAME OF GILEAD PHARMASSET LLC

…… the Applicants

And

IN THE MATTER OF A REPRESENTATION BY WAY OF AN OPPOSITION UNDER SECTION 25(1) AND RULES 55 THERETO BY Virupaksha Organics Limited, having address at B-4, IDA, Gandhinagar, Hyderabad; Telangana State – 500037, India.

…… the Opponents

REPRESENTATION BY WAY OF OPPOSITION U/S 25(1)

1.0 It is respectfully submitted a Pre-grant Opposition Under Section 25(1) of the Patent Act, 1970 as amended by The Patents (Amendment) Act 2005 and Rule 55(1) of the Patent Rules, 2003 as amended by the Patents (Amendment) Rules 2006, is hereby presented by the Opponents against Indian Patent Application No. 3658/KOLNP/2009 (hereinafter referred to as the "Opposed Application") in the name of Gilead Pharmasset LLC (hereinafter referred to as Applicant).

2.0 OPPONENTS BUSINESS AND ACTIVITIES

The opponent is a Company incorporated under the laws of India and carries on business, inter alia, of manufacture of various Active Pharmaceutical Ingredients / Drug Intermediates. The Opponent has access to the latest technologies relating to manufacture of the drugs and medicines. The Opponent is a manufacturer of pharmaceutical products. The Opponent is also engaged in the developments of medicinal and pharmaceutical products.

3.0 GROUNDS OF OPPOSITION

The application is opposed on the following grounds:

- Section 25(1)(b): Prior publication
  that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim—
  (i) in any specification filed in pursuance of an application for a patent made in India on or after the 1st day of January 1912; or
  (ii) in India or elsewhere, in any other document.

- Section 25(1)(e): Obviousness/lack of inventive step
  that the invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step, having regard to the matter published as mentioned in clause (b).

- Section 25(1)(g): Insufficiency
  that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

- Section 25(1)(h): Failure to disclose information or furnishing false information relating to foreign filing
  that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which is in any material particular was false to his knowledge.

4.0 DOCUMENTS CONSIDERED IN THE ANALYSIS

The present representation by way of Opposition U/S 25(1) takes into consideration the following documents:

Document 1 [D1] - WO 2005/003147 A2 assigned to Pharmasset

(priority: May 30, 2003; published on Jan 13, 2005)

Document 2 [D2] - WO 2005/012327 A2 assigned to Univ Cardiff (priority: July 21, 2003; published on February 10, 2005)

Document 3 [D3] - Journal of Medicinal Chemistry, 2005, Vol 48, 5504-5508; (published by Pharmasset Ltd on July 26, 2005).

Document 4 [D4] - Journal of Medicinal Chemistry, 2007, 50, 1840-1849; published by Cardiff University on March 17, 2007.

Document 5 [D5] - WO 2001/092282 A2 assigned to Idenix (priority: May 26 2000; published on December 06, 2001)

Document 6 [D6] - Mini-Reviews in Medicinal Chemistry, 2004, 4, 371-381; published by Cardiff University on May 1, 2004

Document 7 [D7] - Antimicrobial Agents and Chemotherapy, 2005, 1898-1906 published by Gilead

Document 8 [D8] - FEBS Letters 1994, 351, 11-14, published by Cardiff University.

Document 9 [D9] - Antiviral Research 35, 195-204, 1997, published by Cardiff University

5.0 ANALYSIS OF THE IMPUGNED APPLICATION

Patent Application No. 3658/KOLNP/2009 entitled "Nucleoside Phosphoramidate Prodrugs" in the name of Gilead Pharmasset LLC is filed on October 20, 2009 claiming priority from US Provisional applications US 60/909,315 dated March 30, 2007, US 60/982,309 dated October 24, 2007 and US Patent Application 12/053,015 dated March 21, 2008. IN '3658 is a national phase of WO 2008/121634 which is filed on Mar 26, 2008 and published on October 9, 2008 and the impugned application was published in the official journal dated March 19, 2010 (u/s 11(A)).

The impugned application pertains to a Nucleoside Phosphoramidate Prodrugs, which are generally used for treating viral diseases; further the impugned application specifically claims Sofosbuvir which is a Nucleotide Polymerase Inhibitor and inhibits the RNA polymerase that the hepatitis C virus uses to replicate its RNA.

As admitted by applicants, 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.

According to the applicant, 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.

The applicant also admitted that 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.

To overcome the drawback, the alleged invention provides stable phosphate prodrugs which are hydrolyzed by enzyme to produce a nucleoside monophosphate wherein the rate limiting initial phosphorylation is avoided.

6.0 CLAIMS OF THE IMPUGNED APPLICATION

The impugned application was filed initially with 80 claims; further the applicant has amended the total no of claims to 14 after the RFE is filed.

The present application is not filed in accordance with corresponding international application (WO 2008/121634 A2). The applicant/agent has entered in India with less number of claims and fees, which is violation of section 138(4) along with rule 7(2)(c) of the Act. As per section 138(4) along with rule 7(2)(c) the title,

description, claim, and abstract and drawing, if any, filed in international application shall be taken as complete specification in India.

Request for examination of this application is filed on March 21, 2011. There are total 14 amended claims, filed on Dec 26, 2011. Claims 1 and 8 are independent claims and claims 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14 are dependent claims.

Claim 1
(S)-2-{[(2R,3R,4R,5R)-5-(2,4-Dioxo-3,4-dihydro-2H-pyrimidin-1-yl)-4-fluoro-3-hydroxy-4-methyl-tetrahydro-furan-2-yl-methoxy] phenoxy-phosphorylamino}-propionic acid isopropyl ester or a stereoisomer thereof (Specific product claim).

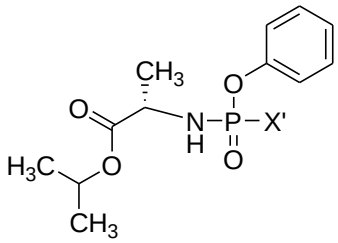
Claim 2
A composition comprising the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium.

Claim 3
A composition for treating a hepatitis C virus, which comprises an effective amount of the compound or a stereoisomer thereof as claimed in claim 1 and a pharmaceutically acceptable medium.

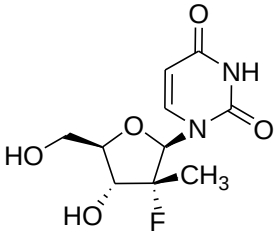
Claim 4
A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

Claim 5
A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound or a stereoisomer thereof as claimed in claim 1.

Claim 6
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'.



Compound 4"



Compound 5'

X' is a leaving group.

Claim 7

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'

Claim 8

(S)-isopropyl-2-(((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2yl)methoxy)(phenoxy) phosphoryl)amino)propanoate.

Claim 9

A composition comprising the compound as claimed in claim 8 and a pharmaceutically acceptable medium.

Claim 10

A composition for treating a hepatitis C virus, which comprises an effective amount of the compound as claimed in claim 8 and a pharmaceutically acceptable medium.

Claim 11

A method of treating a subject infected by a virus, which comprises: administering to the subject an effective amount of the compound as claimed in claim 8; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

Claim 12

A method of treating a hepatitis C virus infection in a subject in need thereof, which comprises: administering to the subject an effective amount of the compound as claimed in claim 8.

Claim 13
A process for preparing the compound as claimed in claim 8, said process comprising: reacting a compound 4" with a nucleoside analog 5'.

Claim 14
A product comprising the compound as claimed in claim 8 obtained by a process comprising: reacting a compound 4" with a nucleoside analog 5'.

6.1 Summary of Impugned Claims:

Claim 1 of the impugned application is directed to a compound which is known by its generic name as Sofosbuvir or its isomer. According to the Indian Patent Law it is now required that the applicant should disclose the generic name of the product in the application; wherein the generic name of the claim 1 is not disclosed in the impugned application.

Claim 2 is directed to a composition comprising compound claimed in claim 1 and a pharmaceutical acceptable medium. However, there is support found to evaluate the word "medium".

Claim 3 is directed to composition for treating a hepatitis C virus using compound claimed in claim 1 and a pharmaceutically acceptable medium.

Claim 4 is directed to MOT a subject infected by a virus using compound of claim 1; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

Claim 5 is directed to MOT hepatitis C virus infection using compound of claim 1.

Claim 6 directed to a process for preparing a compound of claim 1.

Claim 7 is directed to a product by process claims.

Claim 8 is specifically directed to Sofosbuvir.

Claim 9 is directed to a composition comprising Sofosbuvir and a pharmaceutically acceptable medium.

Claim 10 is directed to a composition for treating Hepatitis C virus using an effective amount of Sofosbuvir and a pharmaceutically acceptable medium.

Claim 11 is directed to MOT a subject infected by a virus using Sofosbuvir; wherein the virus is selected from among hepatitis C virus, West Nile virus, a yellow fever virus, a dengue virus, a rhinovirus, a polio virus, a hepatitis A virus, a bovine viral diarrhea virus, and a Japanese encephalitis virus.

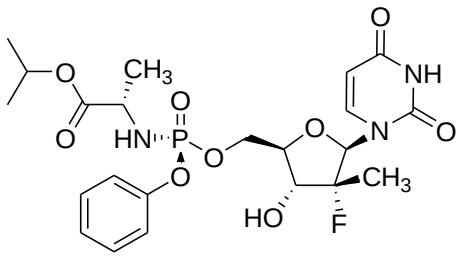
Claim 12 is directed to MOT hepatitis C virus infection using Sofosbuvir.

Claim 13 directed to a process for preparing a compound of Sofosbuvir.

Claim 14 is directed to a product by process claims.

7.0 SOFOSBUVIR PRODUCT INFORMATION

Sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase. It has a molecular Formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. Sofosbuvir is chemically known as (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl) methoxy)-(phenoxy)phosphorylamino)propanoate. It has the following structural Formula:



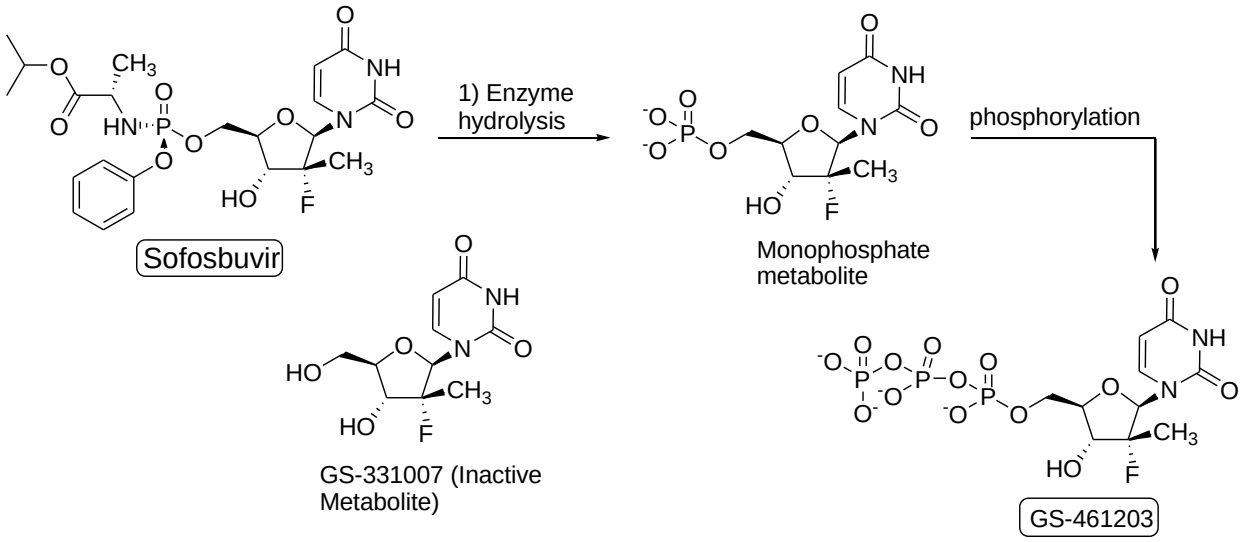
Sofosbuvir

7.1 Mechanism of Sofosbuvir:

Sofosbuvir is a prodrug which is developed by using Protide Technology. Sofosbuvir is metabolized to form the pharmacologically active nucleoside analog triphosphate GS-461203 specifically 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-triphosphate. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalysed by human cathepsin-A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. Dephosphorylation results in the formation of nucleoside metabolite GS-

331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.

The Metabolic Pathway can be shown in the scheme given below:

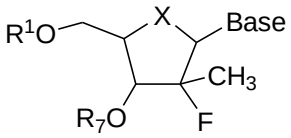


In the above shown metabolic pathway it is understood that Sofosbuvir is prodrug which is converted to triphosphate metabolite which is an active form of Sofosbuvir.

8.0 BRIEF DESCRIPTION OF THE PRIOR ART PROCESSES

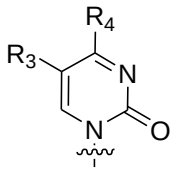
8.1 Document 1 [D1]:

[D1] claims and discloses several (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides which are useful in the treatment of HCV; wherein the nucleosides are generically represented by compound of Formula A.



Formula A

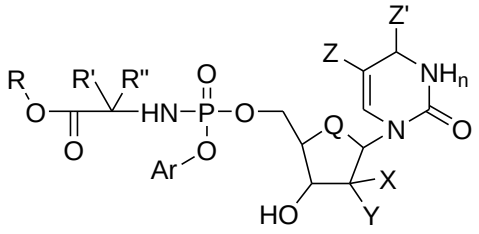
Base is



X is O; R_1 is phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug;
R_7 is H;
R_3 is H;
R_4 is OH.

Document 2 [D2]:

[D2] claims a compound of Formula II or a pharmaceutically acceptable derivative or metabolite; which generically covers various Nucleoside phosphoramidates and are used in the treatment of cancer.

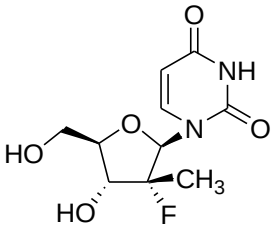


Formula II

wherein R is alkyl, R' and R" are independently selected from the group comprising H, alkyl, Q is O, X and Y are selected from F and methyl; Ar is a monocyclic aromatic ring moiety, Z is H, Z' is =O; with the proviso that, except where R is 2-Bu-(-CH_2-$CH(CH_3)_2$) and one of R' and R" is H and one of R' and R" is methyl (-CH_3), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl (-C_6H_5).

Document 3 [D3]:

[D3] is an article published in 2005; this article discloses hydroxy metabolite of Sofosbuvir which is represented by compound of Formula I.

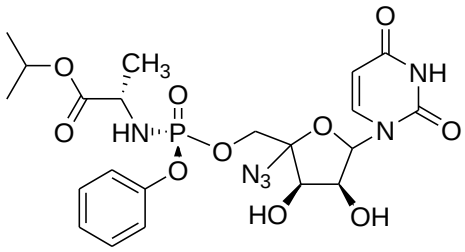


Formula I (Hydroxy Metabolite of Sofosbuvir)

This article also discloses the use of compound of Formula I in the treatment of Hepatitis C virus.

Document 4 [D4]:

This article discloses a process for the preparation of 2′,3′-O,O-Cyclopentylidene-4′-Azidouridine 5′-O-[Phenyl(isopropyloxy-L-alaninyl)] Phosphate which is represented by compound of Formula 1:

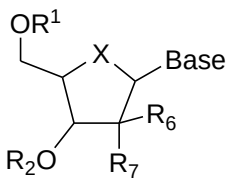


Formula 1

This article teaches a process for the preparation of active HCV polymerase Inhibitors from inactive nucleoside.

Document 5 [D5]:

[D5] claims and discloses different 2' and 3'-nucleoside prodrugs for treating Flaviviridae infections; further [D5] claims a compound of Formula I'; which generically discloses Hydroxy and phosphate metabolites of Sofosbuvir.



Formula I'

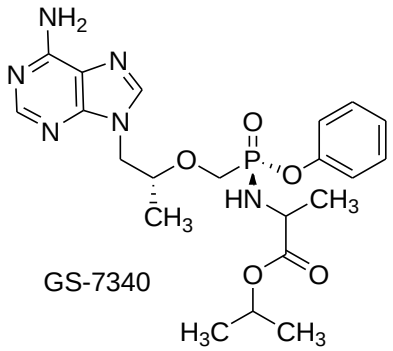
Base is a pyrimidine base R_1 is phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug;
R_2 is H;
R_6 is fluoro;
R_7 is lower alkyl

Document 6 [D6]:

This article discloses the development of aryl phosphoramidates, their mechanism of action and structure-activity relationships. This article generally discloses (2S)-isopropyl-2-(((phenoxy)phosphoryl)amino)propanoate as a prodrug moiety.

Document 7 [D7]:

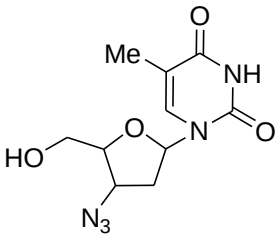
This article generically discloses a process for the preparation of isopropylalaninyl monoamidate phenyl monoester prodrug of Tenofovir (GS 7340) and its *in vitro* antiviral activity, metabolism, and pharmacokinetics were determined. This article also discloses anti-HIV-1 activity (EC_{50}), cytotoxicity (CC_{50}), and in vitro metabolic stabilities of Tenofovir and Tenofovir prodrugs.



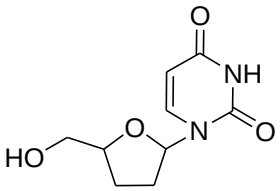
GS-7340

Document 8 [D8]:

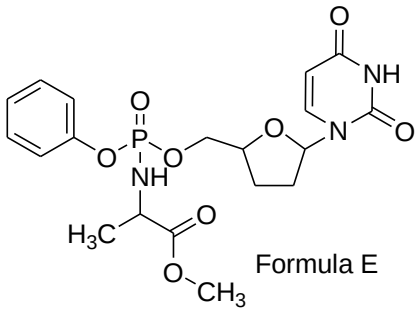
This article discloses phosphoramidate derivatives of dideoxy uridine (ddU) which are active against HIV. This article specifically discloses anti-HIV nucleosides and their analogs which are given below:



Formula C



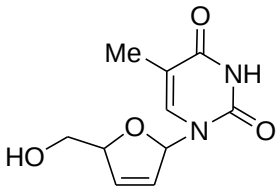
Formula D



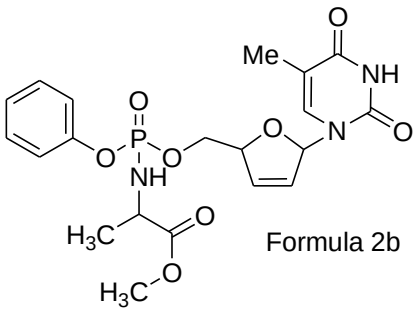
Formula E

Document 9 [D9]:

This article discloses phosphoramidate derivatives of the nucleoside analogs, and specifically discloses 2',3'-dideoxy-2',3'-didehydro thymidine as potential membrane-soluble pro-drugs which are given below:



Formula 2a



Formula 2b

9.0 ANALYSIS OF CLAIMS OF ALLEGED INVENTION

As discussed below, the independent claims:

- Claims 1 to 14 are not novel under Section 25(1)(b) over the disclosure in Document [D1] and [D5].
- Claims 1 to 14 are obvious and do not have inventive steps under Section 25(1)(e) over the disclosure in Documents [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8] and [D9].

10.0 GROUNDS CONSIDERED FOR OPPOSITION

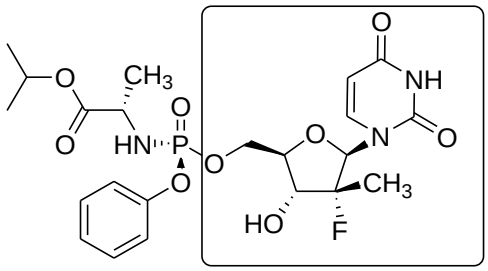
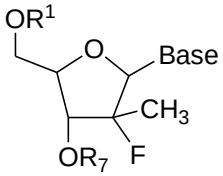
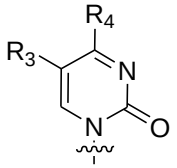
I) Lacks Novelty Under Section 25(1)(b):

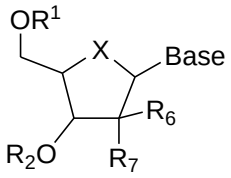
The alleged invention is not novel and are not patentable under section 25(1)(b) of the Patent Act, 1970 as amended in 2005. The claims of the alleged invention are

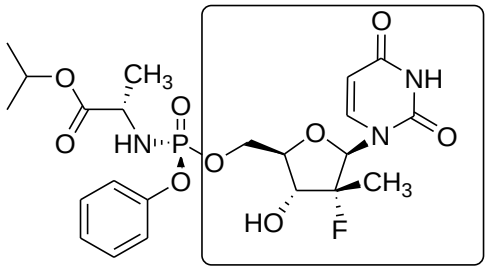
inherently anticipated over the disclosure in WO 2005/003147 A2 (hereinafter referred to as [D1]) which is published on January 13, 2005, much earlier than the priority of the impugned application filed by Pharmasset Ltd.

[D1] discloses basic chemical moieties which represents 2'-deoxy-2'-fluoro-2'-C-methyl nucleosides and methods for the treatment of Flaviviridae infections, especially hepatitis C virus (HCN).

10.1 Given below is the detailed comparison of claims of the impugned application with the disclosure of [D1] and [D5]:

Invention claimed in IN '3658	**Invention disclosed in [D1]**
Claims 1 & 8: (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 or a stereoisomer thereof. 	➢ [D1] claims and discloses various (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides; wherein claim 10 of [D1] relates to a compound of Formula A  Formula A Base is  R_1 is phosphate, including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; R_7 is H; R_3 is H; R_4 is OH. [D1] page 31 defines prodrug such as phosphate ester, salt of an ester or a related group and a compound that is metabolized, for example hydrolysed or oxidized, in the host to

	form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, animated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. [D1] page 46 further discloses 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.
Invention claimed in IN '3658	**Invention disclosed in [D5]**
Claims 1 & 8: (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 or a stereoisomer thereof.	➢ [D5] claims and discloses various nucleosides derivatives; wherein the claims of [D5] relates to a compound of Formula I; which is represented as:  Formula I Base is a pyrimidine base R_1 is phosphate,

	including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug; R_2 is H; R_6 is fluoro; R_7 is lower alkyl [D4] page 51 defines word prodrug such as an ester, phosphate ester, salt of an ester or a related group of a nucleoside compound which, upon administration to a patient, provides the nucleoside compound. Pharmaceutically acceptable prodrugs refer to a compound that is metabolized, for example hydrolyzed or oxidized, in the host to form the compound of the present invention. Typical examples of prodrugs include compounds that have biologically labile protecting groups on a functional moiety of the active compound. Prodrugs include compounds that can be oxidized, reduced, aminated, deaminated, hydroxylated, dehydroxylated, hydrolyzed, dehydrolyzed, alkylated, dealkylated, acylated, deacylated, phosphorylated, dephosphorylated to produce the active compound. The compounds of this invention possess antiviral activity against flavivirus or pestivirus, or are metabolized to a compound that exhibits such activity.

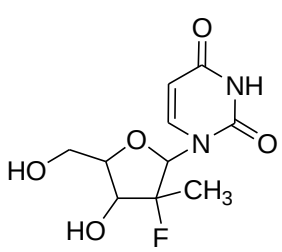
From the above comparison claims 1 to 14 of the alleged invention are anticipated by disclosure of [D1] and [D5]. [D1] & [D5] discloses a Markush structure of 2-deoxy nucleosides which encompasses thousands of compounds which are useful for the treatment of viral diseases.

The structure of Sofosbuvir comprises a pyrimidine (uracil) base attached to a sugar moiety containing fluoro and methyl at 2nd position and a phosphoramidate group at 5th position.

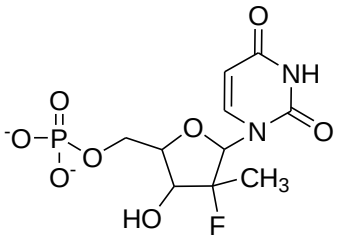
According to the impugned specification and the reported mechanism of Sofosbuvir the following statements cane be made:

i) Sofosbuvir is a stable phosphoramidate prodrug which is used for the treatment of viral diseases.
ii) Sofosbuvir is hydrolyzed and phosphorylated to its triphosphate metabolite through monophosphate metabolite

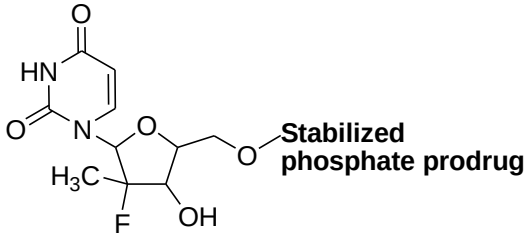
[D1] & [D5] discloses phosphate, diphosphate and triphosphate derivatives of nucleosides; based on the disclosure the following compounds can be derived.



Formula I



Formula b



Formula a'

[D1] page 51 also discussed on the Stereoisomerism wherein the compounds disclosed in the [D1] can be isolated in optically active and racemic forms. Hence, the claims of the impugned application lacks novelty over the disclosure of [D1] and [D5] and claims 1-14 have to be rejected over the disclosure of [D1] & [D5].

II) Lack of Inventive step and Obvious Under Section 25(1)(e) and 2(1)(ja):

The invention claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step over the disclosures of [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8] & [D9] which all are available in the public domain before the priority date of the impugned application.

The use of nucleosides and their analogs in the treatment of viral diseases is already known. Nucleosides can be used as therapeutic drugs, which include a range of antiviral products used to prevent viral replication in infected cells.

The most commonly used nucleoside drugs include:

Deoxyadenosine analogues:

- Didanosine (ddI)(HIV)
- Vidarabine (chemotherapy)

Adenosine analogues:

- BCX4430 (Ebola)

Deoxycytidine analogues:

- Cytarabine (chemotherapy)
- Emtricitabine (FTC)(HIV)
- Lamivudine (3TC)(HIV, hepatitis B)
- Zalcitabine (ddC)(HIV)

Guanosine and Deoxyguanosine analogues:

- Abacavir (HIV)
- Aciclovir
- Entecavir (hepatitis B)

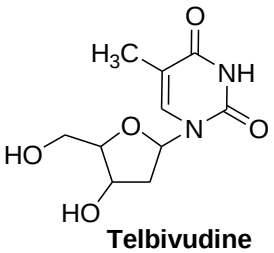
Thymidine and deoxythymidine analogues:

- Stavudine (d4T)
- Telbivudine (hepatitis B)
- Zidovudine (azidothymidine or AZT)(HIV)

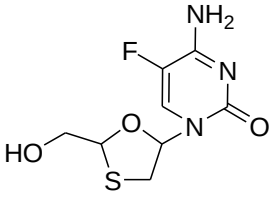
Deoxyuridine analogues:

- Idoxuridine
- Trifluridine

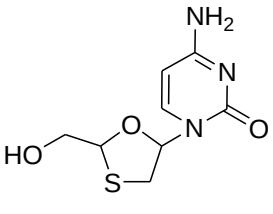
The following given drugs are used in the treatment of Hepatitis B virus and other diseases.



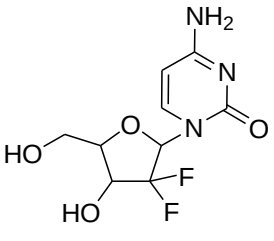
Telbivudine



Emtricitabine



Lamivudine

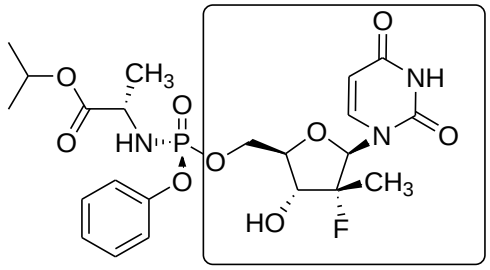
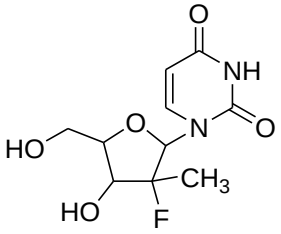


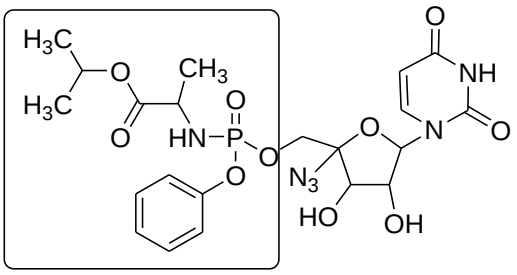
Gemcitabine

The alleged invention is a simple routine experimentation to a person skilled in the art and it is obvious over the disclosures of [D2], [D3], [D4], [D6], [D7], [D8] and [D9]; which all are available in the public domain before the priority date of the impugned application.

10.2 Given below is the detailed comparison of claims of the impugned application with the disclosure of [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8] & [D9]:

Invention claimed in IN '3658	**Invention claimed & disclosed in [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8]**

	& [D9]
Claims 1 & 8: (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 or a stereoisomer thereof. 	➢ [D1] & [D5] claims and discloses various (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides; which are discussed in comparison table 1. From the disclosures of [D1] & [D5] the following compound of Formula I can be derived  Formula I The compound of Formula I is a hydroxy metabolite of Sofosbuvir which does not undergoes phosphorylation which is a key step for the conversion of Sofosbuvir to its active metabolite. Hence, it is inactive. *(Refer page 22 of WC500160597).* ➢ [D3] discloses compound of Formula I' and its Cytidine analog as potent inhibitor of HCV replication. ➢ [D3] discloses anti-HCV activity of compound of Formula I'; which is represented in EC values; which are given below: **cpBVDV[a] (MDBK cells)** | **HCV replicon[b]** EC_{90} (μM)[b] | CC_{50} (μM)[b] | EC_{90} (μM) | CC_{50} [c] (μM) >100 | >100 | >100 | >100 ➢ [D4] discloses phosphoramidate

	approach to convert inactive uridine nucleosides to active nucleosides. ➢ This article specifically discloses prodrugs of 4-azidouridine and their anti-HCV activity; wherein the 4-azidouridne is represented by compound of Formula 1.  Formula 1 The above compound of Formula 1 is tested and the $EC5_0$ (μM) value is given as 0.77. ➢ [D2], [D6], [D7], [D8] and [D9] teaches 2-(((phenoxy)phosphoryl)amino) derivatives as prodrug moieties to activate the parent nucleoside drugs which all are published before the priority date of the alleged invention.

Section 25(1)(e) states invention so far as claimed in any claim of the complete specification is obvious and clearly does not involve any inventive step.

Section 2(1)(ja) states "inventive step" means a feature of an invention that involves technical advance as compared to the existing knowledge or having economic significance or both and that makes the invention not obvious to a person skilled in the art.

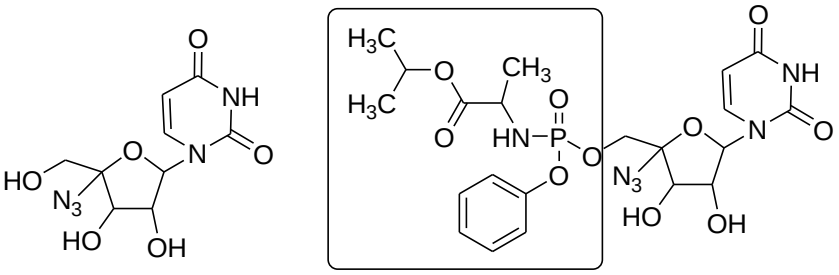
In-view of above sections and the discussed prior art which is filed before the priority date of IN '3658; the claims of alleged invention are obvious to a person skilled in the art.

The claimed invention does not involve any inventive step over [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8] & [D9]:

[D1] discloses compound of Formula A and its phosphate derivatives.

[D3] discloses of compound of Formula I which is a nucleoside moiety of the claimed compound of the opposed patent application. [D3] also discloses the therapeutic activity of compound of Formula I which is given as >100 (EC_{50} (μM))

[D4] teaches the protide approach which involves the preparation of L-alanine-phenyl-phosphoramidate isopropyl ester prodrug of inactive nucleoside. [D4] also discloses the therapeutic activity of 4-Azidouridine nucleoside and its phenyl phosphoramidate Protide.

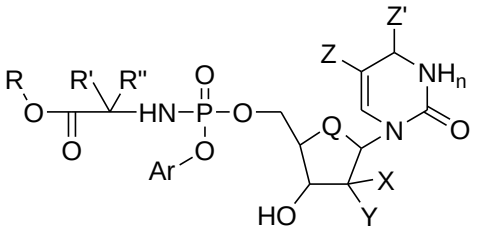


4-Azidouridine **Protide of 4-Azidouridine**

According to the disclosure of [D4] the Anti-HCV activity of 4-Azidouridine is >100 (EC_{50} (μM)) and the Anti-HCV activity of protide of 4-Azidouridine is reported as 0.77. Hence, from [D4] one can understand that a Protide approach is used to increase the therapeutic activity of inactive nucleoside.

The teachings in [D3] and [D4] motivate a person skilled in the art to combine those teachings to derive the claimed subject matter with a reasonable expectation of success. Hence, the claims of IN '3658 is obvious and lacks an inventive step over the [D3] and [D4].

[D2] teaches the preparation of 2-(((phenoxy)phosphoryl)amino) propanoate as a prodrug moiety to activate the inactive parent nucleoside drug for the treatment of cancer. However, the alleged invention is nothing but a new use of known substance.



Formula II

R is alkyl, R' and R" are independently selected from the group comprising H, alkyl, Q is O, X and Y are selected from F and methyl; Ar is a monocyclic aromatic ring moiety, Z is H, Z' is =O; with the proviso that, except where R is 2-Bu-(-CH_2-

$CH(CH_3)_2$) and one of R' and R" is H and one of R' and R" is methyl ($-CH_3$), when n is 1 and X and Y are both H, then Ar is not unsubstituted phenyl ($-C_6H_5$).

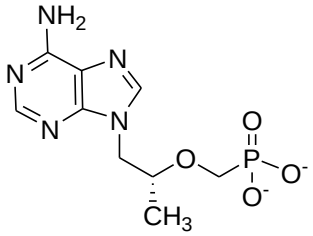
[D6] discloses the discovery and SAR of phosphoramidate triesters of a range of antiviral nucleosides. This article synthesized a series of Aryloxy Phosphoramidates and discloses their potential activity.

This article has disclosed that A 10-20 fold boost in anti-HCV potency was noted on phosphoramidate formation from Adenine base nucleoside; alkenyl Adenine nucleosides such as were also studied wherein the free compounds with free OH group were reported as inactive, whereas the phosphoramidate of the above compounds were active.

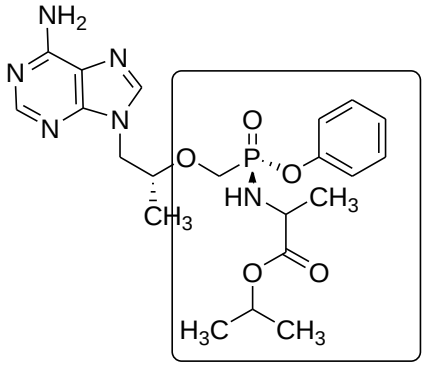
From [D6] one can understand that the protide approach is used to increase the therapeutic activity of inactive nucleoside.

Hence, the claimed invention does not involve an inventive step and it is obvious over the teachings in [D3] and [D6].

[D7] discloses the therapeutic activity of Tenofovir and its prodrugs. The structure of GS-7340 which is a prodrug of Tenofovir is given below:



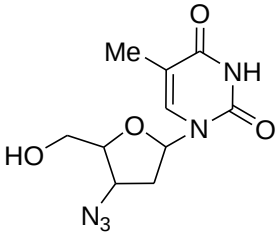
Tenofovir



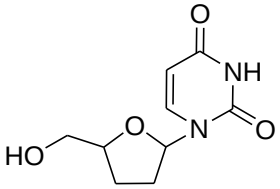
GS-7340

[D7] further discloses anti-HIV activity of Tenofovir and its Prodrug GS-7340 wherein the $EC_{50}{}^{a}$ (μM) of Tenofovir is reported as 5.0 ± 2.6 and $EC_{50}{}^{a}$ (μM) of GS-7340 is reported as 0.005 ± 0.002.

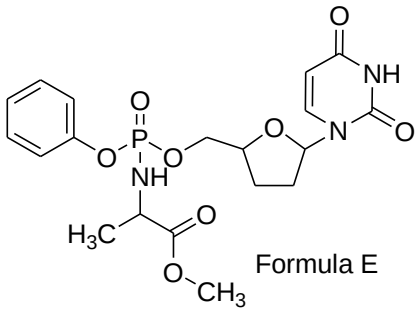
[D8] discloses phosphoramidate derivatives of dideoxy uridine (ddU) which are active against HIV. This article specifically discloses anti-HIV nucleosides and their analogs which are given below:



Formula C



Formula D



Formula E

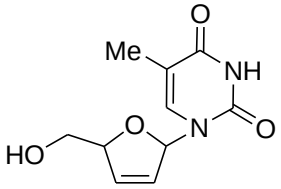
Further this article demonstrated anti-HIV activity of parent nucleosides such as compounds of Formula C & D and their phosphate derivatives; according to the disclosure the parent nucleoside compound of Formula D is active only at the higher concentrations; hence, it can be considered as inactive nucleoside; wherein the phosphate derivate of Formula D such as compound of Formula E shows 50-times more active than the parent nucleoside *(Refer page 13)*.

The anti-HIV activity of compound of Formula D and its phosphate derivative Formula E is given below:

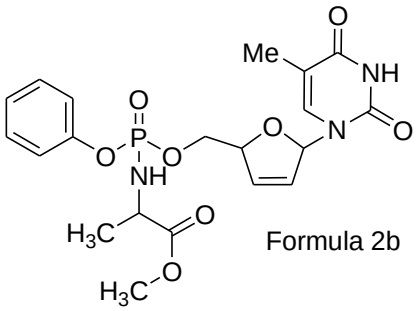
Compound	C8166		JM	
	ED_{50}	CC_{50}	ED_{50}	CC_{50}
D	200	>1.000	1.000	>1.000
E	4	400	20	500

From the above data it is clear that Protide prodrug strategy is a common knowledge which is generally applied to activate the active triphosphates of an inactive nucleosides.

[D9] discloses phosphoramidate derivatives of the nucleoside analogs, and specifically discloses 2',3'-dideoxy-2',3'-didehydro thymidine as potential membrane-soluble pro-drugs which are given below:



Formula 2a



Formula 2b

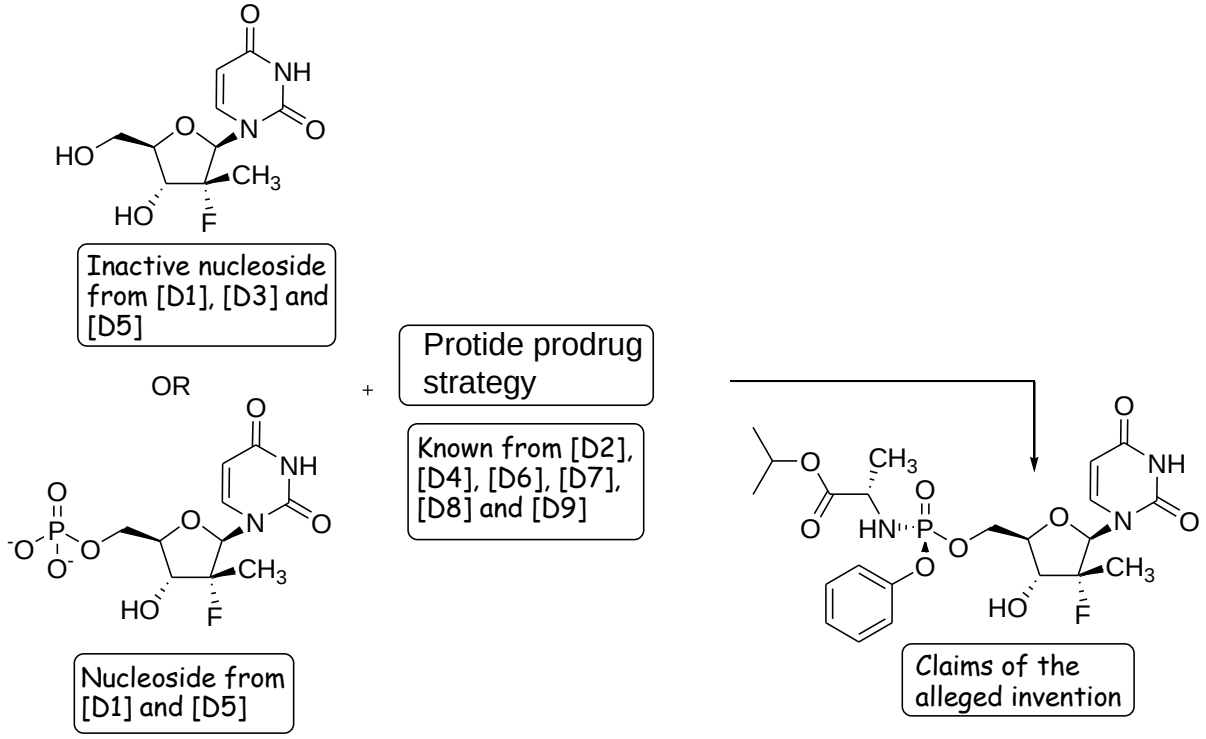
The antiviral activity of the above compounds were demonstrated and this article states that Formula 2b was noted to retain full activity in the TK^- cell line and it was 300 times more potent than compound of Formula 2a (Refer Page 199).

The following table represents Anti-HIV and MSV activity and cytotoxicity of compounds of Formula [2a], [2b] in CEM cell cultures

Compound	EC50 (μM) CEM/O HIV-1	EC50 (μM) CEM/O HIV-2	EC50 (μM) CEM/TK$^-$ HIV-2	CC_{50} (μM) CEM/O	EC_{50} (μM) C3H/3T3 MSV	MIC (μM) C3H/3T3
2a	0.36	0.27	25	≥100	1.62	>100
2b	0.085	0.102	0.075	>100	11.0	>100

From the above data it is clear that Protide prodrug strategy is a common knowledge which is generally applied to activate the active triphosphates of an inactive nucleosides.

The claims of the alleged invention is just a routine experiment for an ordinary person over the teachings of [D1], [D2], [D3], [D4], [D5], [D6], [D7], [D8] and [D9]; which is represented schematically as:



From the above references it can be understand that the protide approach is a common method to increase the therapeutic activity of inactive nucleoside. Hence, a person skilled in the art starting from [D1], [D3] and [D5] applying the teachings any of [D2], [D4], [D6], [D7], [D8] and [D9] will arrived to the subject matter of claims of the impugned application. Hence, the invention claimed in IN '3658 is obvious and it can be anticipated over the teachings of the above prior art.

III. Subject of any claim of the complete specification is not an invention within the meaning of this Act, or is not patentable under this Act:

a) Falls with in the scope of 3(d):

Section 3(d) states:

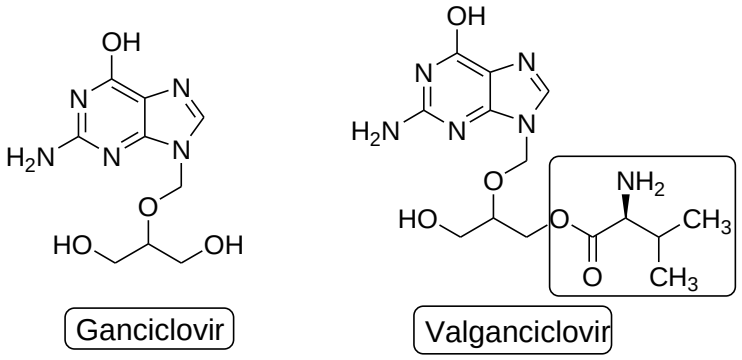
the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.

Explanation-For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.

The compounds claimed in complete specification of the impugned application are nothing but derivatives of the compounds disclosed in [D1] and [D5]. The Impugned application claims Sofosbuvir or its stereoisomer which is nothing but an ester of the compound disclosed in [D1] and [D5]. Hence, claims 1, 7, 8 & 14 are not patentable under section 3(d).

In Re IN 207232 which claims Valganciclovir:

Valganciclovir is a Prodrug of Ganciclovir invented by Hoffmann-La Roche which is filed in India with the application number IN 959/MAS/1995 on July 27, 1995 having the priority date as July 28, 1994; and the above said application was granted on June 29, 2007 with IN 207232.



Ganciclovir Valganciclovir

There were several Post-grant oppositions filed for the above said patent by Indian Network of Positive People, the Tamil Nadu Network of Positive People, the Delhi Network of Positive People and generic companies (Ranbaxy, Cipla, Bakul Pharma, Matrix) and the Patent Controller had revoked the patent on grounds that it was obvious and did not satisfy the requirements of Section 3(d) of the Patents Act, 1970.

Further, Roche challenged the decision by way of an appeal to the IPAB (OA/28/2010/PT/CH & OA/28/2010/PT/CH) which came up for hearing on 30 January, 2014; wherein the Order was issued to set aside the impugned order and remand the matter to the Assistant Controller of Patents and Designs, Chennai for reconsideration of the matter afresh. Further, in Oct 2014 the same opponents has filed the opposition to reject the patent application and any patent granted thereon may be revoked. Hearing was held on December 22, 23, 2014 and January 21, 2015 and no decision is given on the validity of the prodrug claims.

a) Falls with in the scope of 3(e):

Section 3(e) states that:
A substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance.

Claims 2, 3, 9 and 10 relates to a composition comprising Sofosbuvir or its stereoisomer. The components of this composition do not act in a synergistic manner. Hence, the above said claims of are not patentable under this section.

b) Falls with in the scope of 3(i):

Section 3(i) states that:
Claims 4, 5, 11 and 12 relates to MOT which are not patentable under this section.

IV) Claims are not patentable Under Section 25(1)(g):

The alleged invention claims Sofosbuvir which contains 6 stereogenic centers with a specific configuration. The impugned specification has not provided any specific process for the preparation of Sofosbuvir.

Examples 5-8 discloses a process for the preparation of methyl ester analog of Sofosbuvir. The impugned specification provided examples 13-54 and 56-66 as a table which covers Sofosbuvir and not disclosed any enablement for the

preparation of these compounds. Further, it states that the above compounds are prepared as per the process disclosed in example 5-8.

Example 81 discussed about the separation of diastereomers using a Chiralpak-AS-H (2×25 cm) column under Supercritical Fluid Chromatography (SFC) conditions using 20% methanol in carbon dioxide as solvent. However, there is no exemplification found for the separation of Sofosbuvir which is a stereoisomer.

In view of the above points the complete specification of the impugned application is insufficient and does not describe the best mode of performing the invention.

The skilled person would have known that the synthesis of nucleosides is often complicated, as a result of the number of chiral centers in the sugar ring and the number of reactive functional groups attached to the sugar (which might give rise to unwanted reactions and which would therefore need masking with suitable protecting groups). Hence, it is difficult to a person skilled in the art to prepare Sofosbuvir and its isolation as a specific enantiomer. Further, there is no enablement found in the specification in order to support the claims. Hence, such claims should not be granted.

Further, IN 6087/DELNP/2005 claims metabolites of Sofosbuvir which is also filed by Gilead Pharmasset, LLC on December 12, 2005 which is a national phase of WO 2005/003147 filed on April 21, 2004. The above said is rejected by the controller on Jan 13, 2015 on the grounds of obviousness and lack of inventive step.

V) Failure To Disclose Details Of Corresponding Foreign Applications-Section 25(1)(h):

The controller should verify that the information of corresponding application in other application in other countries have been correctly provided and if not the patent application should be rejected under section 8.

Prayer for Relief:

In view of the above said references Opponent prays as follows:

i) IN 3658/KOLNP/2009 filed by Pharmasset Inc has to be rejected under section 25(1).

ii) the Opponent may be allowed to file further documents as evidence if necessary to support their averments.

iii) the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed.

iv) the Opponent may be allowed to make further submissions in case the application makes any amendments in the claims.

v) any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this Twenty third (23rd) day of May 2015.

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