

The Patents Act, 1970 (As Amended in 2005)

(Section 15)

In the matter of Application no. 6087/DELNP/2005 filed in India on 27/12/2005
for Grant of Patent; Corresponding International Patent Application No. PCT/US2004/012472, dated 21/04/2004,
Claiming Priority Date 03/05/2003, USA;

Applicants:- M/S GILEAD PHARMASSET, INC, USA

Applicants Attorneys: M/S K& S PARTNERS, GURGAON, INDIA

ATTORNEY'S PRESENT FOR ARGUMENT: MS PRATIBHA SINGH, MR. D.C.GABRIEL & MR AMRISH TIWARI

EXAMINER: DR SUNIL GAUTAM, EXAMINER, PATENT OFFICE, NEW DELHI, INDIA

Date of Hearing: 24/07/2014

DECISION

[A] An application titled as "A (2'R)-2'-DEOXY-2'FLUORO-2'-C-METHYL NUCLEOSIDE" was filed in the Patent office, New Delhi on 27/12/2005 for Grant of the Patent. The details of the application are mentioned herein below:

S.NO	Detail of the application	Dates of activity
1	Application No 6087/DELNP/2005	filed on 27/12/2005
2	International application no PCT/US2004/012472	filed on 21/04/2004
3	Priority country USA	Date of priority 30/05/2003
4	publication U/S 11(A)	09/05/2008
5	Form 18 filing done by.....APPLICANT HIMSELF	26/05/2006
6	FER & Last Date for compliance of objection U/S 21(1)	06/04/2009 & 06/04/2010
7	Date of reply to the FER	18/03/2010
8	SER	07/05/14 AND NOTICE OF HEARING U/S 14 07/05/14 WITH DOH 24/07/2014
9	Date of hearing U/S-14	24/07/2014

[B] The claims filed initially were 131 in nos. A FER was prepared and sent to the party with the following objections:-

Serial Number	Objections
1	Distinguishing features as compared with prior art given is not clear and should be provided. The complete specification does not provide the advantages of the claimed invention vis a vis drawbacks of the compositions already known in the prior art.
2	Reference to foreign patent applications/patents should be replaced by Indian patent numbers
3	Claims 1-131 not clear in respect of the expression such as indicated therein.
4	Claims 1- 131 not clearly worded
5	Claims 1-131 do not sufficiently define the invention.
6	Title is not precise and does not sufficiently indicate the subject.
7	A Concise summary of the invention alongwith precise title should be filed in accordance to Rule 13(7) of PA, 1970, amendment 2005.
8	Subject matter of claims lack novelty and inventive step under section 2(1)(j) of Patents Act, 1970, Amendment 2005 in view of all documents cited in ISR/IPRP and 1) BEERS M.H.; BERKOW R. (EDS).: "MERCK MANUAL OF DIAGNOSIS AND THERAPY (17th ed.)" 1999 , MERCK RESEARCH

LABORATORIES , WHITEHOUSE STATION N.J. XP002187299 236240 page 379, column 2, paragraph 2 -page 380, column 1, paragraph 1

2)MARCHAND, ARNAUD ET AL: "Stereospecific synthesis of unnatural.beta.-L-enantiomers of 2-chloroadenine pentofuranonucleoside derivatives" J. CHEM. SOC., PERKIN TRANS. 1 (1999), (16), 2249-2254 , XP001052612

3)VON JANTA-LIPINSKI, MARTIN ET AL: "Newly Synthesized L-Enantiomers of 3"-Fluoro-Modified ss-2"-Deoxyribonucleoside 5"-Triphosphates Inhibit Hepatitis B DNA Polymerases But Not the Five Cellular DNA Polymerases.alpha.,.beta.,.gamma.,.delta., and.epsilon. Nor HIV-1 Reverse Transcriptase" J. MED. CHEM. (1998), 41(12), 2040-2046 , XP001052614

4)VERRI, ANNALISA ET AL: "Relaxed enantioselectivity of human mitochondrial thymidine kinase and chemotherapeutic uses of L-nucleoside analogs" BIOCHEM. J. (1997), 328(1), 317-320 , XP001058113

5)LIN T-S ET AL: "Synthesis of Several Pyrimidine I-Nucleoside Analogues as Potential Antiviral Agents" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 51, no. 4, 23 January 1995 (1995-01-23), pages 1055-1068, XP004104973 ISSN: 0040-4020

6)LIN, TAI-SHUN ET AL: "Design and Synthesis of 2",3"-Dideoxy-2",3"-didehydro-.beta.-L- cytidine (.beta.-L-d4C) and 2",3"-Dideoxy-2",3"-didehydro-.beta.-L-5- fluorocytidine (.beta.-L-Fd4C), Two Exceptionally Potent Inhibitors of Human Hepatitis B Virus (HBV) and Potent Inhibitors of Human Immunodeficiency Virus (HIV) in " J. MED. CHEM. (1996), 39(9), 1757-9 , XP001052613

7)MANSOUR, T. S. ET AL: "Stereochemical aspects of the anti-HCMV activity of cytidine nucleoside analogs" ANTIVIRAL CHEM. CHEMOTHER. (1995), 6(3), 138-42 , XP001058115

8) WO 0009531:relates to a method for treating a host infected with hepatitis B comprising administering an effective amount of an anti-HBV biologically active 2"-deoxy-p-L-erythropentofuranonucleoside or a pharmaceutically acceptable salt or prodrug thereof, wherein the 2"-deoxy-p-L-erythro-pentofuranonucleoside has the formula : EMI50.1 BASE RO OH 0 wherein R is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative ; and BASE is a purine or pyrimidine base which may be optionally substituted.

9) WO 0191737 relates to A method for treating a host infected with hepatitis D virus comprising administering an effective treatment amount of 2"-deoxy-ss-L-erythro-pentofuranonucleoside of the formula: EMI60.1 or a pharmaceutically acceptable salt thereof, wherein RI is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base that may optionally be substituted.

10) EP 0352248 L-ribofuranosyl nucleoside analogues of the formula <CHEM> wherein B is adenine, guanine, hypoxanthine, 2,6-diaminopurine or <CHEM> R<1> is H, F; R<3> is H, OH, F, N3, CN or R<1> and R<2> together constitute a chemical bond; R<3> is OH or <CHEM> wherein n is 0, 1 or 2; R<4> is OH, NH2; R<5> is H, CH3 or C2H5,with certain provisos, in the form of a mixture of alpha and beta anomers or in the form of an alpha or beta anomer for use in therapy in pharmaceutical compositions for therapeutic or prophylactic treatment of infections caused by HIV-viruses, hepatitis B virus or herpes viruses.

11)EP 0285884-relates to a novel process to produce 2",3"-dideoxynucleosides such as, for example, 2",3"-dideoxycytidine, in high yields. More particularly, the various stereoisomers of 2",3"-dideoxynucleosides are obtained. The alpha - and beta -(L)-2",3"-dideoxynucleosides and certain alpha -(D)-2",3"-dideoxynucleosides are obtained as stereochemically pure compounds not heretofore obtained. The compounds so produced are useful as antiviral and antibiotic agents.

12) WO 9613512-This invention relates to alpha and beta L-ribofuranosyl nucleosides, processes for their preparation, pharmaceutical compositions containing them, and methods of using them to treat various diseases in mammals.

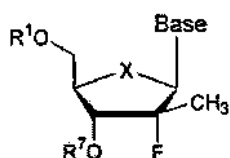
There are a lot of documents available, which relate to the claimed subject matter. The novel features of the invention in view of all the above cited documents need to be characterized in claim 1. The inventive feature of the invention in view of all the above cited documents needs to be defined in claim 1 to establish the inventive step.

9 Claims 1-131 fall(s) within the scope of such clause (d) of section 3 of Patents Act,1970,amendment 2005.There are many prior art citations(as mentioned above) which disclose compounds of the invention.In view of this the efficacy data (as to what is the improvement of the compounds of the invention in relation to prior art compounds) needs to be provided.

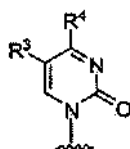
	<p>Claims 16-30 fall(s) within the scope of such clause (e) of section 3 of Patents Act,1970,amendment 2005.Ratio of all the ingredients needs to be defined to establish synergism of the composition.</p> <p>Claims 46-61 fall(s) within the scope of such clause (i) of section 3 of Patents Act,1970,amendment 2005.</p> <p>Claims 61-126 fall(s) within the scope of section 2(1)(j) of of Patents Act,1970,amendment 2005 since no process or product is defined.</p>
10	Claims 1-131 appear to show multiplicity. Kindly note,the claim relates to compounds which are showing many substituted groups,for ex. "X" in the claim relates to a number of varied groups(S,O or NH.....).It is not clear from the specification whether the inclusion of these groups would provide the same effect.
11	Application number should be given in form-3 & form-5.
12	Details regarding application for Patents which may be filed outside India from time to time for the same or substantially the same invention should be furnished within Six months from the date of filing of the said application under clause(b) of sub section(1) of section 8 and rule 12(1) of Indian Patent Act.
13	Details regarding the search and/or examination report including claims of the application allowed, as referred to in Rule 12(3) of the Patent Rule, 2003, in respect of same or substantially the same invention filed in all the major Patent offices such as USPTO,EPO and JPO etc., along with appropriate translation where applicable, should be submitted within a period of Six months from the date of receipt of this communication as provided under section 8(2) of the Indian Patents Act.
14	Extraneous matter (marginal number, PCT application no etc.) should be deleted in specification.
15	Application No. should be given on drawing sheets.
16	Complete International preliminary examination report should be filed as only first page of PCT/IB/373 has been received.
17	Abstract should be filed with a title, concise summary of the invention and within 150 words according to Rule 13(7) of The Patents Rules, 2003.

As a reply to the FER the applicants came up with the twenty claims. The same are reproduced herein below :

1. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) or its pharmaceutically acceptable salt of the structure:



wherein the Base is a pyrimidine base represented by the following formula

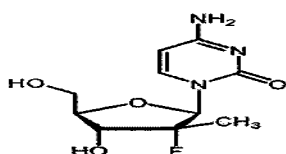


X is O; R¹ and R⁷ are independently H, a monophosphate, a diphosphate, a triphosphate, a H-phosphonate, a Ct-Cto alkyl, a Ct-C\0 alkyl'sulfonyl, a phenyl Ct- C10 alkyl sulfonyl, a biphenyl Ct-C\0 alkyl sulfonyl, or a naphthyl C1-C10 alkyl sulfonyl; and R³ isH and R⁴ is NH₂ or OH.

2. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (13-D or 13-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R⁷ is H and R¹ is a monophosphate, a

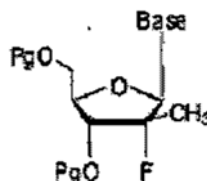
diphosphate, or a triphosphate.

3. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (13-D) as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R^7 is H and R^1 is a diphosphate or a triphosphate.
4. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^7 is H and R^1 is a triphosphate.
5. The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R^1 and R^7 are H.
6. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (13-D) or its pharmaceutically acceptable salt thereof of the formula:



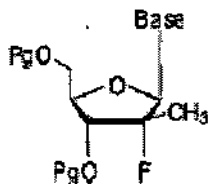
7. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
8. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 2 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
9. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 3 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
10. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 4 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
11. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 5 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
12. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 6 or its pharmaceutically acceptable salt and a pharmaceutically acceptable carrier.
13. A method of synthesizing the nucleoside as claimed in claim 1, which comprises

glycosylating the pyrimidine with a compound having the following structure:



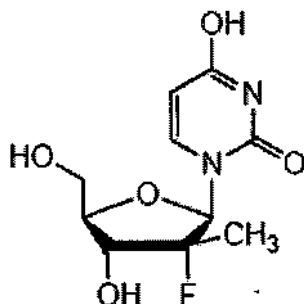
wherein R is C₁-C₄ lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, 8-O-C₁-C₁₀ alkyl, 8-O-phenyl, 8-O-biphenyl, 8-O-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

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



wherein, each Pg is independently a protecting group selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₂, CH₂-C₁-C₁₀ alkenyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂O-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, S-C₁-C₁₀ alkyl, 8-phenyl, SO₂-biphenyl, SO₂-naphthyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

15. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D) or its pharmaceutically acceptable salt thereof of the formula:



16. A pharmaceutical composition comprising about 50 mg to about 2000 mg or more of the nucleoside as claimed in claim 15 or its pharmaceutically acceptable salt and optionally a pharmaceutically acceptable carrier.
17. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 1 and optionally a pharmaceutically acceptable carrier.
18. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 6 and optionally a pharmaceutically acceptable carrier.
19. A liposomal composition comprising liposomes comprising about 50 mg to about 2000 mg or more of the compound as claimed in claim 15 and optionally a pharmaceutically acceptable carrier.
20. A (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (P-D or P-L) or its pharmaceutically acceptable salt substantially as herein described with reference to the accompanying drawings and as illustrated in the foregoing examples.

[C] The Ld. Examiner on re-examination (file note dated 07/05/2014) of the aforesaid amended claims , maintained objections as mentioned below:

Serial Number	Objections
1	<p>Subject matter of revised claims 1-20 lacks novelty and inventive step in view of documents;</p> <p>D1-WO2001/92282 D2-WO0191737 D3-WO2001/90121 D4-WO2002/057425 D5-EP0352248 D6-WO1999/43691 D7-WO2002/18404</p>

D8-WO2002/32920

D9-Perlman et al., J. Med. Chem., 1985, 28, pages 741-748

D10-Schinazi et al., Antimicrobial Agents and Chemotherapy, May 2002, pages 1394-1401

Document D1 discloses the structure in which a sugar attached to a nitrogenous base. Further D1 discloses the Markush Structure of formula XI, XVI, XVII and XVIII. All these formulas provide various options for substitutions and the substitutions discloses that the nitrogenous base may be a purine or a pyrimidine, further several options are provided for the substitution of R1, R6, R7, R9 and R10. From these substitutions it is clear that D1 encompasses compounds similar to the compounds of the present application.

Document D2 discloses a method for treating a host infected with hepatitis D virus comprising administering an effective treatment amount of 2"-deoxy-ss-L-erythro-pentofuranonucleoside of the formula: EMI60.1 or a pharmaceutically acceptable salt thereof, wherein R1 is selected from the group consisting of H, straight chained, branched or cyclic alkyl, CO-alkyl, CO-aryl, CO-alkoxyalkyl, CO-aryloxyalkyl, CO-substituted aryl, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, amino acid residue, mono, di, or triphosphate, or a phosphate derivative; and BASE is a purine or pyrimidine base that may optionally be substituted.

Document D3 also discloses the molecule in which a sugar attached to a nitrogenous base. D3 at formula XI, XVI, XVII and XVIII provides various options for substitutions and the substitutions disclose that the base may be a purine or a pyrimidine, further several options are provided for the substitution of R1, R6, R7, R9 and R10. From these substitutions it is clear that D3 discloses the similar compounds as claimed in the present application. Document D4 discloses the compounds which falls within the scope of present application. The compounds of D4 also discloses a fluoro and an alkyl substitution in the 2" position and a hydroxyl group at 3" position of sugar molecule. The base is selected from the compounds represented by the general structure which appears to be the purine or pyrimidine derivatives.

Document D5 discloses the L-ribofuranosyl nucleoside analogues used for the treatment of infections caused by HIV virus, hepatitis B virus or herpes virus. Document D6 discloses the compounds nucleoside i.e. a nitrogenous base with sugar molecule. These compounds are chemically similar to the general structure of the present application.

Document D7 discloses the derivatives of nucleosides and comprises of a nitrogenous base with a sugar molecule.

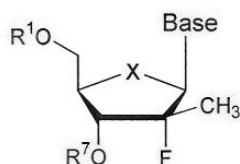
Document D8 discloses modified nucleosides useful for the treatment of viral infections and abnormal cellular proliferation. Document D9 discloses the antiviral activity of 2" -fluoro-5-substituted pyrimidine nucleosides wherein, the 2"-position of sugar molecule is substituted with a fluoro group and 3 "-position is substituted with a hydroxyl group.

Document D10 also discloses such nucleoside analogs wherein the sugar molecules are attached at 2"-position with a fluoro group and 3 "-position with hydroxyl group and the said compounds are known for anti-HIV activity.

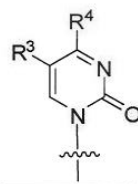
	The above said document teaches the same as claimed in the instant application and therefore considered prejudicial to the novelty and inventive step of the subject-matter of the said claims. In light of the above claims do not constitute an invention u/s 2(1)j of Indian Patent Act as amended.
2	Revised claims 1-6 and 15 are not allowable under section 3(d) since same or similar compounds are already known in the art for similar properties. <i>Derivative</i> of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to known efficacy. There is no such data in the specification that demonstrates such therapeutic efficacy of the claimed compound over the prior art. Claims 13 and 14 are directed to a process for synthesis of the compounds as claimed in claim 1 and therefore these claims are drawn to a mere process without involving any new reactants or resultant products which is also not allowable u/s 3(d). Revised claims 7-12, 16-19 fall u/s 3(e) of the Patents (Amended) Act, 2005 as the said claim defines a mere admixture resulting only in the aggregation of the properties of the components thereof. It is not clear if the combined agents act together to provide a technical effect that is greater than just the sum of the two or more agents alone, or whether the combination is in fact a mere juxtaposition with no interaction of the agents.
3	Claim 20 is not allowable U/S 10(4)(c) of the Patent Act as the claim is unclear, vague and unsearchable.

D] In view of the abovesaid final objection and nature of the objection the attorney were given an opportunity of being heard and to submit their arguments in favour of their application U/S 14. The date of hearing U/S 14 was fixed and DOH was 24/07/2014. MS PRATIBHA SINGH, MR. D.C.GABRIEL & MR AMRISH TIWARI appeared for hearing and submitted arguments in favour of their case. The finally revised claims (total Ten) were also given during the hearing by the applicants agent, the same are reproduced herein below:

1. A nucleoside or its pharmaceutically acceptable salt of the structure:

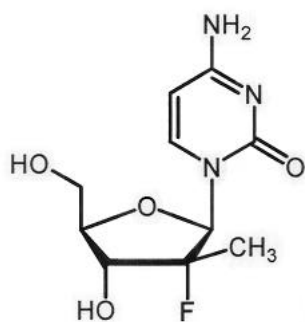


wherein the Base is a pyrimidine base represented by the following formula

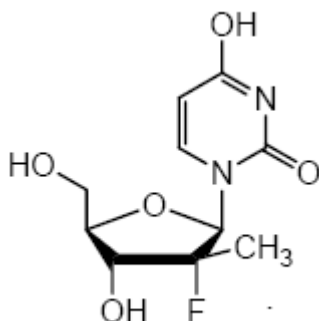


X is O; R¹ and R⁷ are independently H, a monophosphate, a diphosphate, or a triphosphate; and R³ is H and R⁴ is NH₂ or OH.

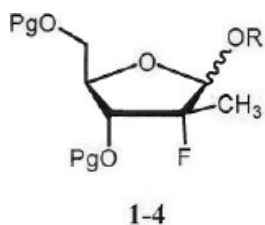
2. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, wherein R⁷ is H and R¹ is a monophosphate, a diphosphate, or a triphosphate.
3. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof, R⁷ is H and R¹ is a diphosphate or a triphosphate.
4. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R⁷ is H and R¹ is a triphosphate.
5. The nucleoside as claimed in claim 1 or its pharmaceutically acceptable salt thereof wherein R¹ and R⁷ are H.
6. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:



7. A nucleoside or its pharmaceutically acceptable salt thereof of the formula:

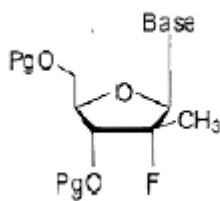


8. A method of synthesizing the nucleoside as claimed in claim 1, which comprises glycosylating the pyrimidine with a compound having the following structure:



wherein R is C₁-C₄ lower alkyl, acyl, benzoyl, or mesyl; and Pg is selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂O-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, SO₂-C₁-C₁₀ alkyl, SO₂-phenyl, SO₂-biphenyl, SO₂-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

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



wherein, each_Pg is independently a protecting group selected from among C(O)-C₁-C₁₀ alkyl, C(O)phenyl, C(O)biphenyl, C(O)naphthyl, CH₃, CH₂-C₁-C₁₀ alkyl, CH₂-C₁-C₁₀ alkenyl, CH₂-phenyl, CH₂-biphenyl, CH₂-naphthyl, CH₂O-C₁-C₁₀ alkyl, CH₂O-phenyl, CH₂O-biphenyl, CH₂O-naphthyl, SO₂-C₁-C₁₀ alkyl, SO₂-phenyl, SO₂-biphenyl, SO₂-naphthyl, *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl, or both Pg's may come together to form a 1,3-(1,1,3,3-tetraisopropylidisiloxanylidene).

10. A nucleoside as claimed in any of the Claims 1 to 7 as and when used for the preparation of a pharmaceutical composition or medicament.

[E] Pre grant oppositions: Two Pregrant Oppositions have been filed against the Grant of the Patent on this application.

(i) first pregrant opposition filed by : M/S Natco Pharma Ltd, Hyderabad through M/S Rajeshwari & Associates on 13/03/2014

Grounds of opposition:

- Section 25(1)(b)/(c): Lack of novelty
- Section 25(1)(e): Lack of inventive step
- Section 25(1)(t): Subject of claims 1 to 20 is not an invention within the

meaning of this Act or is not patentable under this Act

- Section 25(1)g: 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: The Applicant has failed to disclose to the Controller the information required under Section 8.

(ii) Second opposition filed by : Delhi Network of Positive People (DNP+), New Delhi, Initiative for Medicines, Access & Knowledge (I-MAK), Inc, USA through Fidus Law Chamber, New Delhi on 19/6/2014:

Grounds of the opposition:

a) 25(1)(b) - that the invention so far as claimed in any claim of the complete specification has been published before the priority date of the claim.

b) 25(1)(c) - that the invention so far as claimed in any claim of the complete specification published on or after priority date of the applicant's claim and filed in pursuance of an application for a patent in India, being a claim of which the priority date is earlier than that for the applicant's claim

c) 25(1)(e) - 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) or having regard to what was used in India before the priority date of the applicant's claim .

d) 25(1)(f) - that the 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, in particular under sections 3(d).

e) 25(1)(g) - that the complete specification does not sufficiently and clearly describe the invention or the method by which it is performed;

f) 25(1)(h) - that the applicant has failed to disclose to the Controller the information required by S-8 or has furnished the information that in any material particular was false to his knowledge.

[F] ANALYSIS OF THE FINAL CLAIMS IN THE LIGHT OF THE OBJECTIONS MAINTAINED, AND ATTORNEYS ARGUMENT:

It appears from the hearing letter that the following issues on unrevised 20 claims need to be resolved before the grant of the patent on this application:-

- (i) The claims are not novel and inventive in view of the document cited and identified in the hearing letter as D1 to D9. It is noted that the citations D1 (is WO 200192282, priority date of 2001 is equivalent and family member to the cited doc as referred in FER as ISR citation no US 2003060400, Priority date 27/03/2003, hereinafter combinedly D1), D2 (is WO 0191737 same as that of cited in the FER, hereinafter D2) and D5 (is EP0352248 same as that of cited in FER, hereinafter D5) are the same as raised in the

FER whereas D3, D4, D6 to D9 are freshly raised. Therefore D3, D4, D6, D7, D8 and D9 shall not be considered in the proceedings.

- (ii) The Product and process claims fall u/s 3(d) and 3(e).
- (iii) Unrevised claim 20 omnibus claim, is not allowed.

Since the above said three issues of the FER issued under the provisions of the Patent Act, were unresolved the applicant's attorney were given an opportunity of being heard u/s 14 for finalization of the application. Now let us discuss the above said issues in the light of amendments in the claim in the hearing and arguments placed before me by the applicants attorney in favor of their case.

Issue No 1, Novelty and Inventive step: The learned examiner in the subsequent examination report cum hearing letter has raised the objection that the invention is not patentable u/s 2(1)(j).
ARGUMENTS OF THE APPLICANTS AGENT:

Applicants respectfully request the Controller to withdraw the novelty and Inventive Step rejections for at least the following reasons:

- A. The cited references do not disclose or suggest the compounds of the present application;
- B. Seemingly minor changes in substituents at the 2' position of the nucleoside result in large changes in activity and toxicity; and**
- C. Teachings of the prior art did not enable the synthesis of 2'-fluoro (down), 2'-methyl (up) nucleosides.**

We now go into detail on these points.

The Present Invention

The present invention is directed towards pharmaceutical compounds useful in the treatment of Hepatitis C virus (HCV) infection. HCV infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be about 170 million worldwide and about 18 million in India. The present invention is directed to 2'-fluoro (down)-2'-methyl (up) nucleosides and their corresponding mono-, di-, and tri-phosphate forms. These compounds have high levels of activity against HCV, low toxicities, and other favorable characteristics largely because of this unique substitution pattern.

Presently, treatment of HCV infection with Interferons (IFNs) has been commercially available for

the treatment of chronic hepatitis for nearly a decade. Unfortunately, the effect of IFN is temporary and a sustained response occurs in only 8% - 9% of patients chronically infected with HCV (Gary L. Davis. Gastroenterology 18: S104-S114, 2000). Most patients, however, have difficulty tolerating interferon treatment, which causes severe flu-like symptoms, weight loss, and lack of energy and stamina. One more drug, Ribavirin (1- (3-D-ribofuranosyl-1-1, 2, 4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Viriazole (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p1304, 1989). Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV. It has been approved in combination with interferon alpha-2a or interferon alpha-2b for the treatment of HCV. The current therapies using ribavirin and interferon require 48 weeks of treatment—nearly a whole year. Because of the severe side effects and long duration of therapy, many patients do not receive the complete course of therapy and are not cured of this disease.

In light of the fact that HCV infection has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that have low toxicity to the host and that can shorten the duration of treatment.

A. The Cited References Do Not Disclose or Suggest Nucleoside Compounds Having a 2'-Fluoro (down), 2'-Methyl (up) Substitution Pattern.

References D1 – D10 fail to disclose or suggest the compounds of the present application, for at least the reasons given below.

D1-WO2001/92282

According to the Notice, “D1 encompasses compounds similar to the compounds of the present application.”

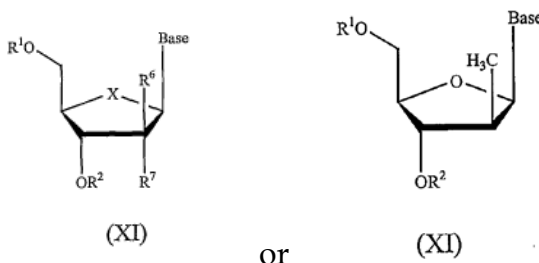
As a preliminary matter, an assertion that compounds in the prior art are “similar” to those in an application is not a proper rejection under a theory of novelty or inventive step. A novelty rejection requires that the exact compound be disclosed. None of the cited references

do so. An inventive step rejection requires a proper and reasoned showing that compounds in the prior art render compounds of the application obvious to a person of skill in the art. Any such argument is lacking in this examination report, and thus the report fails to make a *prima facie* case on inventive step. An “obviousness” argument can be established only by showing such references as may give a person skilled in the art a reason to cause the substitution. In the absence of such a reference, mere similarity in the compounds in a “general” manner does not establish obviousness.

Moreover, the Notice provides no description or bounds of what the term “similar” means. Therefore, the Applicants have no reference as to which compounds of D1 are being asserted against them.

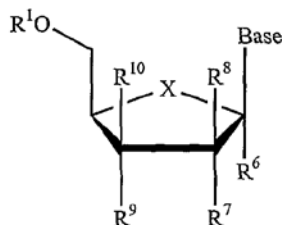
Thus, the mere assertion that compounds in the prior art are “similar” to those of the application is not a proper basis for a rejection under either a theory of novelty or inventive step. Further, as explained below, D1’s compounds are not similar to those of the present application.

Regarding novelty, Applicants direct the Controller to Formula (XI), (XVI), (XVII), and (XVIII):



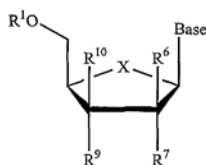
X is O, S, SO₂ or CH₂

R⁷ is hydrogen, OR³, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO₂, NH₂, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)₂, -N(acyl)₂; and



(XVI)

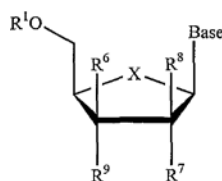
R^7 and R^9 are independently hydrogen, OR^2 , hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-C(O)O(\text{alkyl})$, $-C(O)O(\text{lower alkyl})$, $-O(\text{acyl})$, $-O(\text{lower acyl})$, $-O(\text{alkyl})$, $-O(\text{lower alkyl})$, $-O(\text{alkenyl})$, chlorine, bromine, iodine, NO_2 , NH_2 , $-NH(\text{lower alkyl})$, $-NH(\text{acyl})$, $-N(\text{lower alkyl})_2$, $-N(\text{acyl})_2$;



(XVII)

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

R^7 and R^9 are independently hydrogen, OR^2 , hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, $-C(O)O(\text{alkyl})$, $-C(O)O(\text{lower alkyl})$, $-O(\text{acyl})$, $-O(\text{lower acyl})$, $-O(\text{alkyl})$, $-O(\text{lower alkyl})$, $-O(\text{alkenyl})$, chlorine, bromine, iodine, NO_2 , NH_2 , $-NH(\text{lower alkyl})$, $-NH(\text{acyl})$, $-N(\text{lower alkyl})_2$, $-N(\text{acyl})_2$;



(XVIII)

R^8 is H, alkyl (including lower alkyl), chlorine, bromine or iodine;

alternatively, R^7 and R^9 , or R^8 and R^9 can come together to form a pi bond;

The Controller may note that the R^7 substituent in these compounds does *not* include fluorine. Only chlorine, bromine and iodine were contemplated at this position, suggesting that fluorine was omitted purposefully, a negative teaching or a “teaching away”. As described in the Background section above, the compounds of the present invention have a 2'-fluoro (down) –

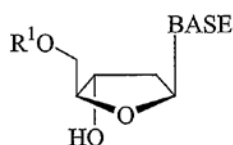
2'-methyl (up) substitution pattern. This substitution pattern is not disclosed in D1. **Further, D1 does not describe how to make a compound with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern or provide any data indicating that such a compound has anti-*flaviviridae* activity, let alone anti-HCV activity.**

Regarding inventive step, the Applicants respectfully assert that no *prima facie* case has been advanced. A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. A prior art reference teaches away when a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Having explicitly excluded fluorine as an option for R⁷, it cannot be said that the person with ordinary skill in the art would have come up with the current solution for the technical problem given the disclosure of D1. As only chlorine, bromine and iodine were contemplated at R⁷ position, suggesting that fluorine was omitted purposefully and it teaches away from the present invention.

The rejections over D1 should therefore be withdrawn.

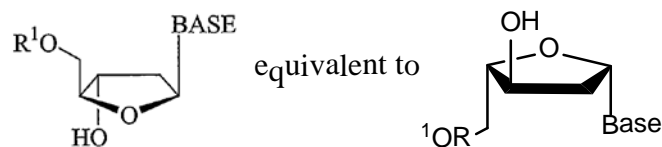
D2-WO0191737

A general structure of the compounds disclosed in the '737 publication is shown below.

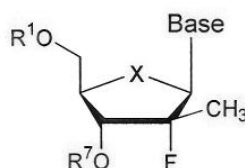


First, compounds of D2 have neither a **fluoro** nor a **methyl** substituent on the ribose ring. In other words, compounds of D2 have no substituents at the 2' position of the ring. These compounds are therefore very different from those of the present application.

Furthermore, the ribose ring of these compounds has a different three-dimensional orientation in relation to the base, -OH, and -CH₂OR¹ substituents than the compounds of the present application (the oxygen of the furanose ring is pointing towards the reader rather than away), as clearly shown here:



in contrast to compounds of the present application:

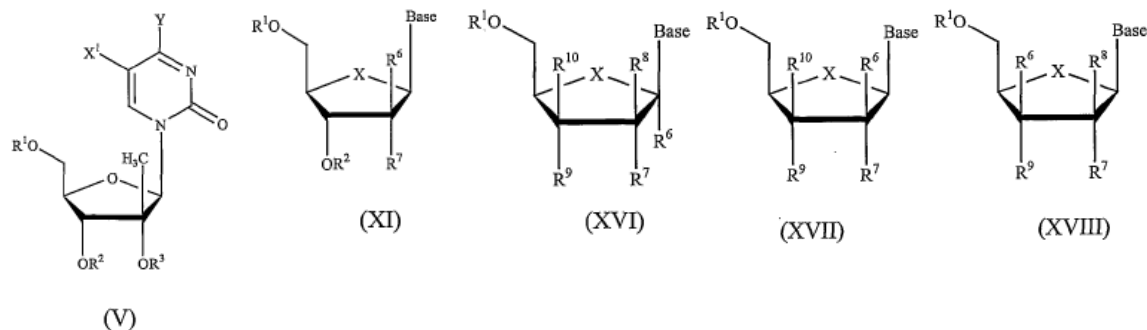


Finally, D2 is directed to methods of treating Hepatitis Delta virus, which is caused by a virus structurally unrelated to the Hepatitis C virus.

These compounds are therefore very different from, and do not disclose or suggest, the compounds of the present application. The rejection over this reference should be withdrawn for at least these reasons.

D3-WO2001/90121

Compounds of D3 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.

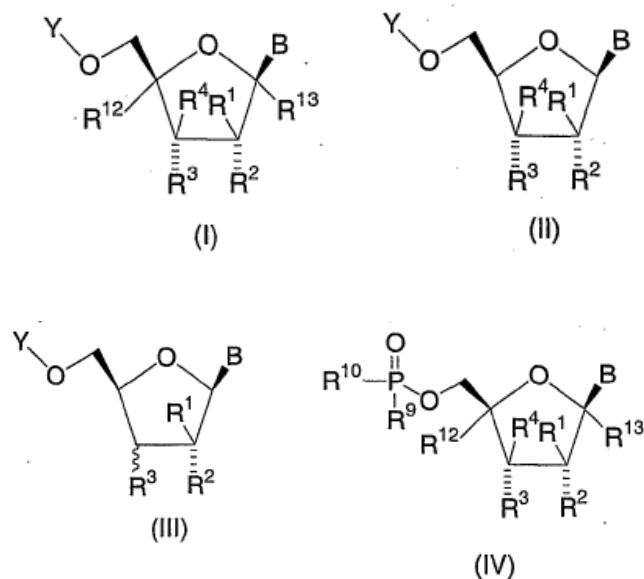


In particular, the R⁷ substituents do not include fluorine. Similar to the compounds of D1, in the compounds of D3 chlorine, bromine and iodine were contemplated at this position, suggesting that fluorine was omitted purposefully. Further, D3 does not describe how to make a compound with a 2'-fluoro (down) – 2'-methyl (up) substitution pattern or provide any data indicating that such a compound has anti-*flaviviridae* activity, let alone anti-HCV activity.

This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D4-WO2002/057425

WO 2002/057425 discloses several general structures, shown here:



The various R substituents can be chosen from a long list of possibilities. The possibilities are shown here, just for for R¹ and R²:

R¹ is hydrogen, C₂₋₄ alkenyl, C₂₋₄ alkynyl, or C₁₋₄ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of R² and R³ is hydroxy or C₁₋₄ alkoxy and the other of R² and R³ is selected from the group consisting of

hydrogen,

hydroxy,

halogen,

C₁₋₄ alkyl, optionally substituted with 1 to 3 fluorine atoms,

C₁₋₁₀ alkoxy, optionally substituted with C₁₋₃ alkoxy or 1 to 3 fluorine atoms,

C₂₋₆ alkenyloxy,

C₁₋₄ alkylthio,

C₁₋₈ alkylcarbonyloxy,

aryloxycarbonyl,

azido,

amino,

C₁₋₄ alkylamino, and

di(C₁₋₄ alkyl)amino; or

R² is hydrogen, C₂₋₄ alkenyl, C₂₋₄ alkynyl, or C₁₋₄ alkyl optionally substituted with amino, hydroxy, or 1 to 3 fluorine atoms and one of R¹ and R³ is hydroxy or C₁₋₄ alkoxy and the other of R¹ and R³ is selected from the group consisting of

hydrogen,

hydroxy,

halogen,

C₁₋₄ alkyl, optionally substituted with 1 to 3 fluorine atoms,

C₁₋₁₀ alkoxy, optionally substituted with hydroxy, C₁₋₃ alkoxy, carboxy, or 1 to 3 fluorine atoms,

C₂₋₆ alkenyloxy,

C₁₋₄ alkylthio,

C₁₋₈ alkylcarbonyloxy,

aryloxy carbonyl,

azido,

amino,

C₁₋₄ alkylamino, and

di(C₁₋₄ alkyl)amino; or

R¹ and R² together with the carbon atom to which they are attached form a 3- to 6-membered saturated monocyclic ring system optionally containing a heteroatom selected from O, S, and NC₀₋₄ alkyl;

D4 cannot be considered novelty destroying for the presently claimed compounds as it does not specifically point out the same substitution pattern of the instant invention. It therefore fails to disclose this element of the invention. First, the R¹ substituent can be chosen from one of hydrogen, C₂₋₄ alkenyl, C₂₋₄ alkynyl, or C₁₋₄ alkyl, each of which may be substituted. There is no specific disclosure or calling out of a methyl group in this position. Second, the R² group may also be chosen from a long list of possibilities; there is no specific disclosure of a “halogen” wherein that halogen is fluorine. Further, there is no preference for any compounds having the same substitution pattern as that of the present invention, and there are no compounds in the Examples section which have the same substitution pattern of the instant invention. Still further, the specification fails to provide any guidance or suggestion as to compounds having the particular 2'-fluoro (down) – 2'-methyl (up) substitution pattern of the instant invention.

Furthermore, reference D4 provides no guidance to persons of ordinary skill in the art concerning the synthesis of nucleosides having a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.

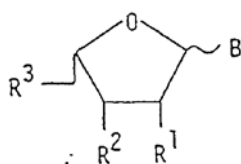
As discussed below, the successful synthesis of nucleosides having a 2'-fluoro (down) – 2'-methyl (up) substitution pattern was extraordinarily difficult.

This reference does not provide the basis for a novelty or inventive step rejection for at least these reasons, and therefore cannot be used to support a rejection on novelty or inventive step.

D4 fails to provide clear and unmistakable directions to the specific combinations

D5-EP0352248

Compounds of D5 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern:

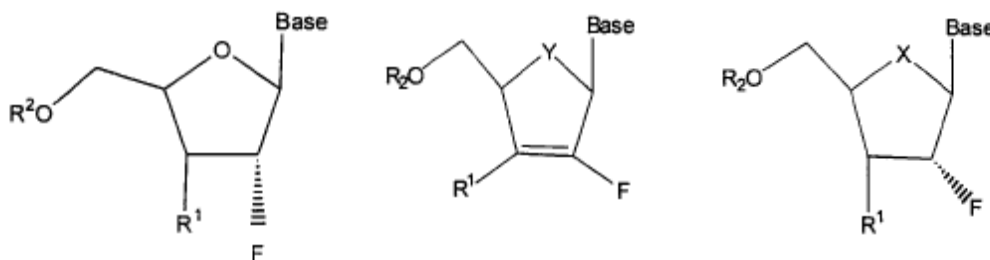


As clearly shown, these compounds are only mono-substituted at the 2' position.

This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D6-WO1999/43691

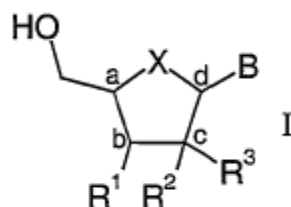
Compounds of D6 also do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern, as clearly seen from the structures.



This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D7-WO2002/18404

Compounds of D7 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.



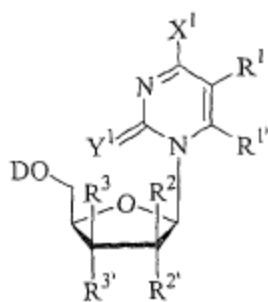
In formula I, (1) R^2 is hydrogen, hydroxyl, alkoxy, chlorine, bromine or iodine and R^3 is hydrogen; (2) R^2 and R^3 together represent $=CH_2$; or (3) R^2 and R^3 represent fluorine. These possibilities do not allow, and therefore do not include, the 2' substitution pattern of the instant invention.

Moreover, D7 provides over 250 preferred embodiments of formula I, the vast majority of which are mono-substituted at the 2' position (position "c") and have $R^2 = -OH$. Only three examples of di-substitutions at the 2' position are provided, and all of these are di-fluoro substitutions (Compounds 242, 243 and 245).

Thus, this reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D8-WO2002/32920

Compounds of D8 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern.



[I-a]

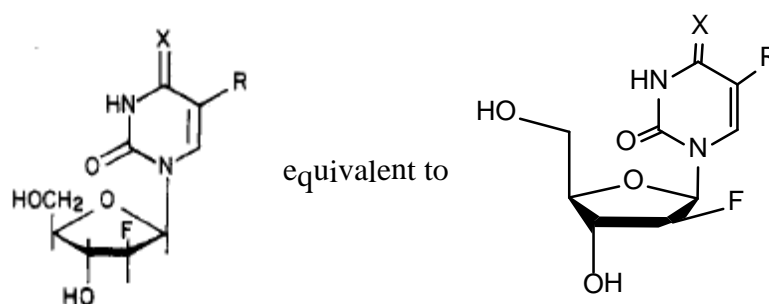
Specifically, the R^2 and $R^{2'}$ positions of formula [I-a] do not include methyl or any alkyl substituent:

each R^2 and $R^{2'}$ independently is hydrogen or halogen (F, Cl, Br or I), OH, SH, OCH_3 , SCH_3 , NH_2 , $NHCH_3$, $CH=CH_2$, CN, CH_2NH_2 , CH_2OH , CO_2H .

This reference therefore does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D9-Perlman et al., J. Med. Chem., 1985, 28, pages 741-748

Compounds of D9 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. First, the “stem” in the drawings of the furanose ring (the vertical lines on the ring where no substituent is specified) refer to hydrogen atoms and not to some other substituent. So at the 2' position for example, this is a 2'-fluoro (up) and 2'- hydrogen (down).



This observation is supported by the chemical name of the compounds. Also, the fluoro substituent at the 2' position is in the “up” position and not in the “down” position.

This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above.

D10-Schinazi et al., Antimicrobial Agents and Chemotherapy, May 2002, pages 1394-1401

Compounds of D10 do not have a 2'-fluoro (down) – 2'-methyl (up) substitution pattern. First, this reference is primarily concerned with compound DPC 817, which does not have substituents at the 2' position and in fact has a double bond between the 2' and 3' carbon atoms.

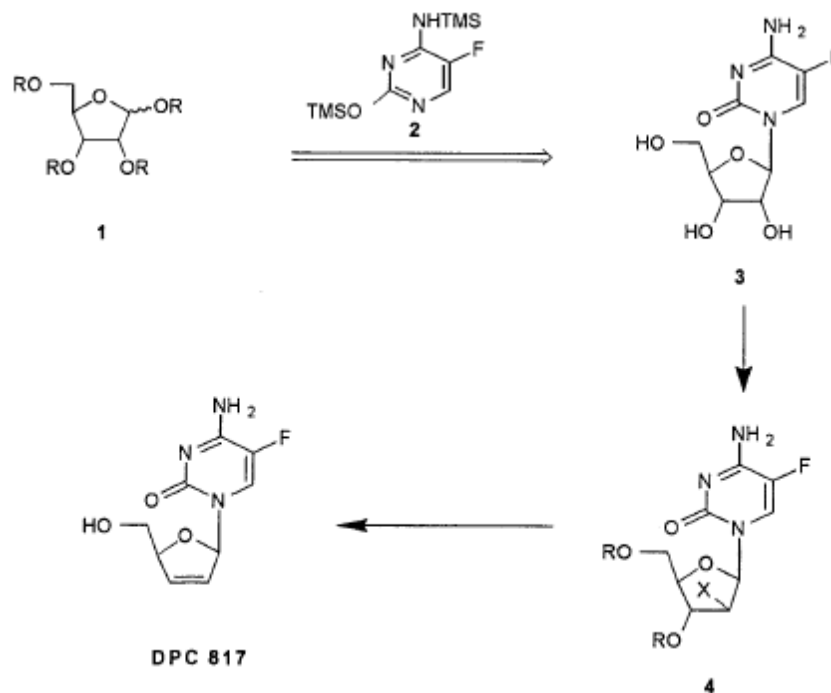


FIG. 1. Synthesis of DPC 817.

Second, the intermediate compounds used to make DPC 817 do not have the substitution pattern of the present application.

Also, this reference regards compounds having activity against the human immunodeficiency virus (HIV), which is a different target than HCV.

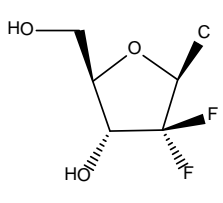
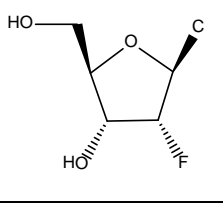
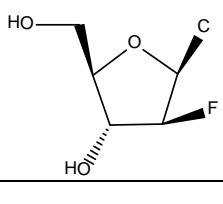
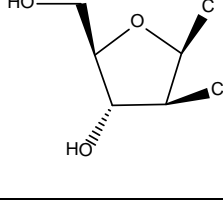
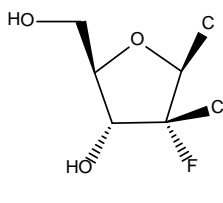
This reference does not provide the basis for a novelty or inventive step rejection for the same reasons as above. In view of the above discussion, it is the Applicant's view that the present invention is in fact novel and the objection under section 2(l)(j) of the Patents Act should be withdrawn.

B. Seemingly Minor Changes in Substituents at the 2' Position of Nucleosides Result in Large Changes in Activity or Toxicity.

The particular substitution pattern of the claimed compounds is unique, and imparts unexpectedly high activity and low toxicity to them.

Applicant re-submits Table 1, which shows activity and cytotoxicity of various 2'-substituted nucleosides. The data for Compound 5 (present invention) is unexpectedly better than the comparator compounds.

Table 1. Activity and Cytotoxicity Comparison of 2'-Substituted Cytidine Analogs

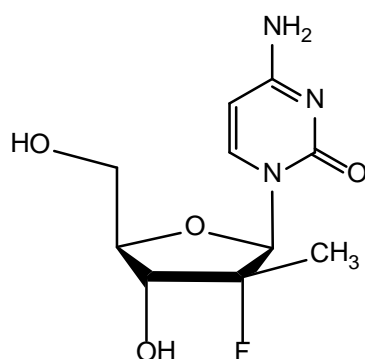
No.	Compound	HCV Activity EC ₉₀ (μM)	Cytotoxicity			
			Clone A CC ₅₀ (μM)	Hep G2 CC ₅₀ (μM)	BxPC3 CC ₅₀ (μM)	CEM CC ₅₀ (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Cannot determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

“C” represents cytosine.

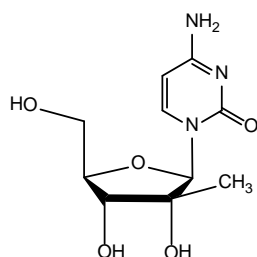
For example, the 2'-fluoro (down) – 2'-hydrogen (up) compound (Compound 2) shows good HCV activity but is also toxic in certain cell lines. The 2'-fluoro (up) – 2'-hydrogen (down) compound (Compound 3) is too toxic to test. The 2'-di-fluoro compound (Compound 1) is very active but also very toxic. Finally, the 2'-methyl (up) – 2'-hydrogen (down) compound (Compound 4) has activity but is also toxic against certain cell lines.

These data show the high degree of unpredictability of these compounds. Compound 5, therefore, has a very unexpected and surprising activity and toxicity profile.

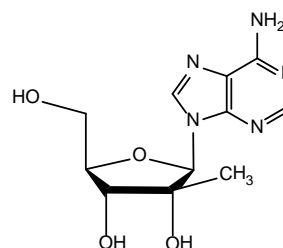
In addition, the learned Controller may refer to the experimental data already disclosed in the specification which clearly indicates that 2'-fluoro (down)-2'-methyl (up) substitution pattern on the nucleoside are non-toxic and bioactive as compared to other nucleoside compounds. Particularly, Tables 1 to 9 of the present application compare activity of (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (compound 5) with 2'-C-methylcytidine and 2'-C-methyladenosine.



(2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine (**compound 5**)



2'-C-methylcytidine



2'-C-methyladenosine

The unexpected properties of Compound 5 cannot be predicted and, thus, could not have been obvious from the other comparator compounds.

As such, Applicants assert that from the data presented above, it is clear that the 2'-fluoro (down)-2'-methyl (up) substitution pattern present in the nucleosides of the present application unexpectedly imparts therapeutic activity against HCV while at the same time exhibiting no toxicity to the host.

In view of above, the compounds of instant invention are novel and not obvious to one skilled in the art. Hence the Applicant respectfully requests the Controller to waive this objection.

C. The Prior Art Did Not Enable the Synthesis of 2'-Fluoro (down), 2'-Methyl (up) Nucleosides.

None of the cited references describe how to make the compounds of the present application.

The current applicant, Gilead Pharmasset LLC (“Gilead”), has successfully defended challenges to corresponding applications in other countries—in particular Norway and the United States—by Idenix Pharmaceuticals, Inc. (“Idenix”). One issue central in these challenges was whether Idenix made 2'-fluoro (down), 2'-methyl (up) nucleosides before the inventor of the Gilead applications did.

Both, the court in Norway and the Patent Trial and Appeal Board (PTAB) of the United States Patent and Trademark Office (USPTO) decided that they did not, and that Gilead was the first to do so.

The Oslo District Court issued a decision on March 21, 2014 (Annex A) which, in part, discussed how difficult it was to make 2'-fluoro (down), 2'-methyl (up) nucleosides. The Oslo District Court wrote

"... the skilled person will be faced with a number of choices that have to be made in order to be able to produce or synthesise [a 2'-fluoro-2'-methyl nucleoside]. Firstly, a choice needs to be made between the sugar route and the nucleoside route. Thereafter, starting materials need to be chosen. Many alternatives will be available in respect of both route alternatives, and the choices will not be perceived as obvious. Moreover, a fluorination reagent needs to be selected. This also involves numerous alternatives. Even if one starts out from the most precise and restrictive part of the description, as well as the alternative claims, there are several options. One may for example choose both natural and synthetic bases. Finally, one needs to select reaction conditions and solvents, etc., for the various reactions. The Court notes that minor variations in chemical processes may have a major impact and be decisive in terms of whether or not one succeeds in bringing about the desired compound." (emphasis added)

Oslo District Court, Case No. 12-155575TVI-OTIR/01 and 13-170456TVI-OTIR/01, 21 March 2014, page 32.

The Court then gave its judgment on whether Idenix made any 2'-fluoro-2'-methyl nucleosides before the priority date of the present application:

"...the skilled person will, in order to carry out the invention, have to find an overall solution that will depend on the sum total of a number of partial solutions. The Court is of the view that the skilled person would not be able to carry out the invention without a considerable amount of trial and error. This conclusion is also supported by the fact that Idenix itself would not appear to have been able to produce the compound until at a much later date."

***Id.*, p. 33.**

The Oslo District Court found the Clark patent to be valid and the Idenix patent to be invalid.

The PTAB of the USPTO reached a similar conclusion: Clark was the first to invent 2'-fluoro (down), 2'-methyl (up) nucleosides.

Testimony by Dr. Victor E. Marquez on this point was important to the decisions of both the Oslo District Court and the PTAB (USPTO). In his testimony for the Norway trial (Annex B), Dr. Marquez described, based on his review of Idenix's internal documents, that Idenix employed a team of Ph.D. chemists and consultants specializing in fluorination chemistry, all of whom were unable to make the 2'-fluoro (down), 2'-methyl (up) nucleosides for a period of over three years. Dr. Marquez noted that these chemists tried at least seven potential chemical routes and 16 different reagents in attempts to make a 2'-fluoro (down), 2'-methyl (up) nucleosides. All of these attempts failed. It was only after the publication of the Clark patent application (corresponding to 6087/DELNP/2005) when researchers at Idenix were finally able to synthesize compounds of this type.

In summary, the applicants request the Controller to withdraw the novelty and inventive step rejections because (A) none of the cited references describe or suggest the same compounds, (B) the compounds have unexpectedly high activity and low toxicity not suggested by the prior art, and (C) prior art did not teach how to make the claimed compounds, as illustrated by Idenix's difficulties.

Thus, it is Applicant's position that (2'R)-2'-deoxy-2'fluoro-2'-c-methyl nucleoside of the present invention remain novel and inventive in view of the cited reference. As such, Applicant respectfully submits that the Examiner's rejection for lack of novelty and inventiveness is improper and should be withdrawn.

D. Corresponding Applications in Many Other Countries Have Been Granted.

The Controller may note that claims similar to those presented here in 6087/DELNP/2005 have been granted in numerous countries (see Form 3 details):

Country	Patent No.
Australia	2004253860
Canada	2527657
China	200480019148.4
Colombia	1214
Indonesia	P0028288
Israel	172259
Israel (Divisional)	210367
Japan	4958158
Japan (Divisional)	5266357
Korea	200883703
Mexico	275935
Malaysia	138477
Norway	0333700
New Zealand	543867
Philippines	1-2005-502136
Russia	2358979
Singapore	117252
South Africa	2005-09521
United States	7429572
United States (Continuation)	8415322

Exemplary claim sets from some of these countries are included in **Annex 3**.

In view of these arguments, the claimed compounds of the instant application are novel and not obvious to one skilled in the art. Hence the Applicant respectfully requests the Examiner to waive these objections.

OBSERVATION:- In respect of novelty & Inventive Step of the present claims 1 to 10 the arguments of the Ld Attorney is agreeable. It has been noticed that learned examiner has raised citation from D1 to D9 in the hearing letter wherein D1, D2 and D5 were similar to the citation raised in the FER for examination of Novelty and inventive step. Therefore only Matching citations of hearing letter and FER are being considered for finalization of this application w.r.t. novelty and inventive step of the invention. The D1 is the closest prior art to this claimed invention. On comparing the finally revised claims from 1 to 10 with citation given in the FER and hearing letter prima facie does not appear to affect the novelty and inventive step of the present set of the claims. This has further been confirmed by grant of patent with similar set of claims in various jurisdictions namely JPO (Patent No. 4958158 and 5266357), US (Patent No 7429572 and 8415322). Therefore I have no hesitation to acknowledge Novelty and Inventive step of the present set of claims.

Issue No 2, Application of Section 3 (d): Ld Exr has raised the non Patentability objection U/S 3(d) in FER & Hearing letter On the basis of cited documents D1, D2 & D5. The arguments of the applicants agent in this regard are reproduced herein below:

ARGUMENTS OF THE APPLICANTS AGENT:

Arguments of the applicants Attorney has been reproduced herein below:

Applicants respectfully ask the Controller to withdraw the rejection over Section 3(d) for at least the following reasons.

A. A Rejection Based on Section 3(d) is Not Applicable

There is a fundamental error in the application of Section 3(d) to the present case. The submissions of the Applicant are as under:

- a. Section 3(d) does NOT apply to all pharmaceutical and chemical inventions;
- b. The provision clarifies its application viz., “**new forms of known substances**” – meaning thereby – there has to be a “known substance”. In the absence of a “known substance” there cannot be a “new form”
- c. The section further clarifies that even “new forms of known substances” are patentable – if significant therapeutic efficacy is shown.

Thus,

- (i) there has to be a known substance;
- (ii) the application has to be for a new form of that substance;
- (iii) that new form in order to be patentable has to demonstrate therapeutic efficacy.
- (iv) Therapeutic efficacy has to be established by means of filing comparative data.

In order for Section 3(d) to have application the first two conditions have to be satisfied. The testing of a product for therapeutic efficacy is only after the first two conditions are found applicable.

The Applicant respectfully submits that Section 3(d) only bars a new form of a known substance which does not result in the enhancement of known efficacy of that substance or a new property or

new use for known substance or new use of a known process. It is submitted that Section 3(d) was designed to make a higher bar of innovation for patentability of new salts, esters, and other derivatives (second generation compounds) of known substances (e.g. pharmaceuticals) unless they differ significantly in properties in regard to efficacy to avoid alterations being made to the FORM of such substances and thus extending market exclusivity of known substances. It is NOT meant to create a higher bar for new substances by deeming all new compounds to be merely derivatives of known compounds.

As discussed earlier in detail that presently claimed compounds are novel and inventive and do not exist in the prior art. The claimed compounds are NOT new forms of known compounds. Thus, it must be concluded that the presently claimed compounds are not salts, esters, ethers, polymorphs, pure forms, particle sizes, isomers, mixtures of isomers, complexes, combinations or other similar simple derivative forms of the reference compounds, thereby, making them totally new compounds with unpredictable properties absent Applicant's invention. As such, these new compounds do not fall within the ambit of Section 3(d). The present improper use of 3(d) attempts to define every new compound as merely a derivative of some known structural chemical core thereby barring patentability, despite the compound's novelty and inventiveness in the unpredictable chemical arts.

The Controller may also refer to Judgment given by Delhi High Court in ROCHE V. CIPLA (Erlotinib Hydrochloride) case, wherein impugned Roche Patent was held valid and Erlotinib was not considered as a mere derivative or new form of known substance Gefitinib (Erlotinib differs from Gefitinib with respect to the substitution of a methyl group with ethynyl at the third meta (3') position). Following were some key findings by the Delhi High Court w.r.t. Section 3(d) and known substance:

“Cipla's challenge to the validity of the impugned patent on it being attracted by section 3(d) did not find favour with the court on account of Cipla failing to meet the positive evidence onus to sustain that challenge. The court observed that Cipla had to prove that IN '774 is the 'new form of an old substance' (the 'old substance' being EP '226) and that Example 51 of EP '226, through further reaction, can result in IN '774 is insufficient to establish 'new form of an old substance' unless proven to be contrary, which none of their witnesses deposed.”

In light of the above, the Applicants submit that the claimed compounds are completely novel and inventive and are not merely new forms (salt, ester, derivative, etc.) of "known substances". Thus, Section 3(d) cannot be applied to the claims of the instant application.

Without prejudice to the submission that Section 3(d) is not applicable, it is submitted that as discussed above, and with respect to Table 1, compounds of the present application have a unique and novel 2'-fluoro (down) – 2'-methyl (up) substitution pattern. This substitution pattern, among other aspects of the compound, imparts both high potency and low toxicity to the compounds. Compounds which differ in the substitution pattern at this same position do not possess the same potency vs. toxicity profile.

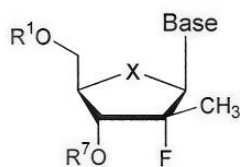
The Controller may note that the Table 1 discloses activity and cytotoxicity data of various 2'-substituted nucleosides. The data presented for the biological profile of Compound 5 (present invention), includes both the intrinsic potency against HCV and cytotoxicity, which exhibits better and unexpected activity over the structurally closest compound. This unexpected activity cannot be predicted based on the structure-activity relationship of related compounds. Further, it is unexpected that appending both a methyl substituent and a fluoro substituent to the 2'-position of a 2'-deoxycytidine nucleoside wherein the methyl substituent is in the β -position (up) and the fluoro substituent is in the α -position (down) would produce a compound (Compound 5) that is both a potent inhibitor of HCV replication in cell culture and lacks cytotoxicity. It is clear that compounds containing either a single fluorine atom in either the 2'- β -position (Compound 3) or the 2'- α -position (Compound 2) or containing di-fluoro substitution at the 2'-position (Compound 1) demonstrate activity against HCV but also show significant cytotoxicity in one or more cell lines tested. In addition, the 2'-deoxycytidine analog (Compound 4) with only a 2'- β -methyl substituent shows substantial cytotoxicity against all cell lines.

In the light of the above, the Applicants submit that the claimed compounds are completely novel and inventive. Thus, Section 3(d) cannot be applied to the claims of the instant application. Hence the Applicants respectfully request the Controller to waive this objection.

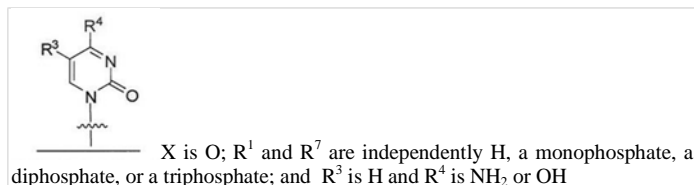
OBSERVATION:- As discussed earlier the citation D1, D2 and D5 cited in the hearing letter are similar to the FER and the closest prior art being D1 as herein before described which discloses the similar compound with changes of orientation of FLUORINE in sugar moiety of the claimed compound(cf comound XI of D1). The change in the orientation of the fluorine downwards in the sugar moiety of claimed compound changes the properties such as lowering of cytotoxicity. This kind of variation of orientation of the groups can make the compound novel and Inventive however, in the eyes of section 3(d) this novel and inventive substance is “ considered to be the same substance, unless they differ significantly in properties with regard to efficacy”. According to the hon'ble SC decision in Novartis AG vs GOI, CA No. 2706-2726/2013 para 180-192, the efficacy means the therapeutic efficacy. Therapeutic efficacy may be proved by showing clinical trials so as to prove significant difference in the properties with regard to efficacy. Therefore the compound XI as disclosed in D1 is the closest prior art as being structurally closed to the presently claimed compound and therefore is the same compound to D1 in the eyes of the section 3(d). Furthermore the compound as disclosed in D1 and in the presently claimed compound are having the same use in the treatment of HCV infection and flavivirus infection . In such circumstances the applicants must

have shown the therapeutic efficacy data to show the significant difference in the properties with regard to efficacy by providing the clinical trials etc. The applicants showed the cytotoxicity data to prove the difference in properties which is insufficient to prove significant increase in the therapeutic efficacy. The data does not show any clinical trials to prove the improvement in the therapeutic efficacy.

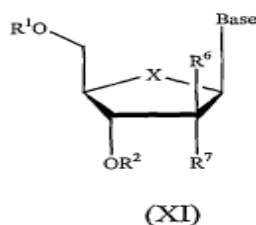
The formula of the claimed compound of this application:



wherein the Base is a pyrimidine base represented by the following formula



The formula of the claimed compound no (XI) of citation D1:



R⁷ is hydrogen, OR³, hydroxy, alkyl (including Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), alkyl), -O(alkenyl), chlorine, bromine, iodine, N(lower alkyl)₂, -N(acyl)₂; and R⁶ is H, OH, R, Azido, Cino, alkenyl, alkyne....Chloro, Bromo, Fluoro, Iodo, NO₂

The applicants submission that for application of sec 3(d) there should be the known substance is not acceptable as the intention of the law comes out from the words "...salts, esters....shall be considered the same substance, unless they differ...". These words clearly shows that the claimed compound may have passed the test of novelty on minor changes in the molecule but to qualify sec 3 (d) which this compound does not show the properties with regard to the therapeutic efficacy". In other words we can say that a molecule with minor changes in addition to the novelty must show significantly enhanced therapeutic efficacy as compared to the nearest prior art molecule which is structurally and functionally close. Similar is the case here, the molecule as claimed in the present application is structurally and functionally similar to the molecule of Document D-1 (XI)th compound may be novel due to the different orientation (stereo isomerism) of the fluoro group in the sugar moiety of the nucleoside but to qualify the requirement of section 3 (d) such novelty must result in significant enhancement of the therapeutic efficacy as compared to the cited molecule D1 compound XI therapeutic properties. The data provided in Table 1 cannot be considered sufficient and appropriate to show the enhancement of the therapeutic efficacy. The judgement of Honourable Delhi court in case of Roche vs Cipla does not apply on this case as

erlotinib and Gefitinib were different in groups by substitution of a methyl group with ethnyl group at the third meta position whereas in the present case the difference lies only in the orientation of fluoro group of compound XI of D1.

In view of all this the claimed compound appears to fall U/S 3(d) of the Patent Act.

The claims 8 & 9 relates to synthesis of the compound as claimed in claim 1 which is in the definition of novelty u/s 2(1)(j) read with section 3(d) has been considered as the same substance to the closest prior art compound of D1. Furthermore, the reactants and reaction conditions are almost similar for the preparation of the compounds of present invention and the closest prior art. Hence the claim numbers 8 & 9 are also not patentable u/s 3(d) as it amounts to mere use of known process which doesn't result in a new product or doesn't employ any new reactant.

The objection u/s 3(e) of the learned examiner maintained in the FER as well as in the hearing letter is considered complied with as in the revised claims 1-10, the composition claims have been deleted.

The objection of non allowance of omnibus claim is complied with as the said claim was deleted by the applicant.

In view of the above discussion herein above the application under consideration with claims 1-10 is not patentable u/s 3(d) of the patent act and liable to be refused .

The applicants plea that the hearing u/s 25(1) should have been appointed inviting both the parties (Opponents and Applicants) in the hearing to decide simultaneously the issues pending in the FER, hearing letter and the issues raised in both the oppositions is not agreeable for the following reason.

Arguments of the applicant:-

Firstly the arguments of the applicant's in this regard must be seen:-

“we would like to submit that whenever there are oppositions filed during the prosecution in an Indian Patent Application, it is practice and precedent that the examination (u/s 14 hearing) and the pre-grant opposition (u/s 25(1) hearing) coincide once all the formalities are fulfilled/over relating to the opposition.

The examination and pre-grant opposition is co-terminus as per the Indian Patent practice and precedent. In UCB Farchim Vs. Cipla, it was held that “.....*This court finds merit in the contention that the pre-grant opposition is in fact “in aid of the examination” of the present application by the Controller.*”

The same had reiterated in Snehlata Gupte Vs. Union of India as below:

“.....The language of Rule 55 (6) leaves no manner of doubt that these two actions i.e. the consideration of the representation and the final decision on the application of Grant of Patent take place simultaneously.”

Further, same has been practiced in many applications where pre-grant opposition has been filed during the prosecution. The various Courts and the Patent office in India held that whenever there are pre-grant Oppositions filed during the prosecution of an Indian Application, both the proceedings i.e. prosecution and Opposition ought to be heard at the same time and order could be passed to conclude the proceedings. Thereafter the Applicant can go to IPAB by way of an Appeal if it so desires. On the other hand, if the pre-grant Opponent is not satisfied with Controller's order they can file post-grant Opposition within one year from the date of grant. The above process involves only one single hearing before the Controller and thereafter the other remedies are open to the Parties as mentioned above. However, if the prosecution hearing is held while a pre-grant opposition is pending, the Controller of Patents cannot grant the Patent since the pre-grant Oppositions is pending and on the other hand, if Controller rejects the Application during prosecution, the Applicant will have to go to IPAB for restoring the application and get the case restored at IPAB and again come before the same Controller for re-opening the case for the Oppositions. Now, the Controller will have to re-open the case as well as pre-grant opposition and follow all the due process of Oppositions and once again hear the matter. By the time, even entire term of the Patent could expire.

The issue is why the Controller should pass two separate orders which may be same or different when the grounds of prosecution and pre-grant Oppositions are more or less same. Hence, coinciding the hearing of prosecution (u/s 14), opposition (u/s 25(1)) saves a lot of time and efforts not only on the part of Controller, but also for all other interested parties.

Further, term of Patent is just twenty years and unlike many other Patent office practices, there is no Patent term extension is available to the Indian Patents Applicants. Filing an Appeal on the Controller's rejection on Opposition during prosecution and getting the case restored and again undergo the pre-grant proceedings before the Controller will be harassment to the Applicant and unduly delay and rob the Applicant's valuable term of the Patent. Furthermore, even one of the opponents is also of the view that prosecution and opposition ought to be co-terminus (see attached letter from Fidus Law Chambers).

OBSERVATION:-

The said application was under the procedure of examination under section 12 & 13 and the objection of the Ld. Examiner was still pending for finalization. To finalise the said pending issues of the FER the Ld. Examiner has recommended hearing u/s 14 to hear the applicant to decide the

grant of Patent. Since the pregrant opposition was filed later to the last date for compliance of all the objection as mentioned in section 21(1) therefore, the process to consider the pregrant opposition was pending till the completion of the procedure of section 12 & 13. For the consideration of pending objections a hearing letter was issued and applicant was heard and wherein decision on this application is the refusal. Pending objections shown in the hearing letter were similar to the objection of the FER and accordingly only the applicant was heard u/s 14. As per rule Opponents could not be involved in the examination procedure, so not heard. Opponents will be involved only on the inception of proceedings under section 25(1). The pregrant opposition effect is infructuous by refusal of this application. However, if procedure of 25(1) read with rule 55 is initiated later, the opponents need to be heard and decision to be issued u/s 25(1) read with section 15. The referred judgement of honourable court in UCB Franchim vs Cipla is not applicable here as it was about the maintaining of appeal in High court or IPAB in respect of decision issued u/s 25(1). Further in this case it has been held "that pregrant opposition is in fact in aid of examination" is true however, this has not barred to work upon the home procedure first. Pre grant opposition filed here is treated as disposed off in favour of Opponent with the refusal of patent application at this point of time.

Second judgement of honourable court in Snehlata Gupte Vs. Union of India quoted by the applicant that the language of Rule 55(6) leaves no manner of doubt that these two actions i.e. the consideration of the representation and the final decision on the application of grant of patent take place simultaneously.

This judgement of honourable court is also not applicable in this case as application of procedure of rule 55 has not been initiated yet. Therefore, the contention of the applicant that hearing u/s 25(1) read with section 14 should have been taken together cannot be accepted.

[E] In view of the above mentioned observations I refuse to proceed for grant of patent on this application.

The documents filed by the opponents as mentioned above will be sent to the applicants alongwith this decision on 14/01/2015 for further processing as per the requirement of the Patent Rules.

The oppositions filed u/s 25(1) by the opponents as mentioned above at present is infructuous with this rejection of the application U/S 15 for further processing of the Patent Grant.

DATED: 13/01/2015

(HARDEV KARAR)
DEPUTY CONTROLLER OF PATENTS & DESIGNS
PATENT OFFICE, NEW Delhi