THE PATENTS ACT, 1970 (AS AMENDED)

&

THE PATENTS RULES, 2003 (AS AMENDED)

SECTION 25(1)

In The Matter of

An Application for Patent No. 201601713899

AND

In The Matter of

A Pre-grant opposition to the grant of a patent thereon under section 25(1)

And

Hearing u/s 14

Merck Sharp & Dohme LLC**…….....The Applicant**
SANKALP REHABILITATION TRUST……**.....The Opponent**

Appeared in the hearing held on January 23, 2025under section 25(1)

Ms.Archana Shanker, Sh.Devinder Singh Rawat, Ms.Vashima Miglani…… **For the Applicant**

Sh G. Deepak Sriniwas , Dr. Shyam Ji Gupta ……...**For the opponent**

1) Lack of Novelty (u/s 25(1)(b)): The Opponent argued that the subject matter of the patent application is not novel and is anticipated by prior art.
2) Lack of Inventive Step (u/s 25(1)(e)): It was contended that the application lacks an inventive step, as the claimed invention would be obvious to a person skilled in the art in light of the prior art.
3) Non-patentability and Not an Invention (u/s 25(1)(f)): The Opponent submitted that the invention does not meet the criteria of patentable subject matter under the applicable patent laws and regulations.

4) Insufficiency of Disclosure (u/s 25(1)(g)): The Opponent argued that the patent application fails to provide sufficient disclosure to enable a person skilled in the art to practice the invention.

Timelines:

a) An application for a patent bearing number 201617031899 was filed in Patent Office on19/09/2016 entitled "4 SUBSTITUTED NUCLEOSIDE DERIVATIVES AS HIV REVERSE TRANSCRIPTASE INHIBITORS". A request for examinationunder section 11-B was filed on **05/10/2016.** As per the provision under Section 11-A of Patents Act, 1970 the said application was published on13/01/2017.

b) The said application was examined under Section 12 and 13 of Patents Act, 1970 and FirstExamination Report (henceforth referred to as FER containing a statement of objection wasforwarded to the applicant on **27/09/2018**.

c) A reply by applicant/ agents to FER was filed on **27/03/2019**.

d) A representation u/s 25(1) of Patents Act, 1970 for opposing the grant of patent applicationno. 201617031899 was filed by **Rajeshwari Hariharan**, Constituted Attorney for the Opponent,RAJESHWARI & ASSOCIATES A – 202, FIRST FLOOR SHIVALIK ENCLAVE MALVIYA NAGAR NEW DELHI – 110017 on behalf of**SANKALP REHABILITATION TRUST**, SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002 on **05/12/2020.**

e) A pre-grant Notice was issued to the applicant on **15/07/2023** via email.

f) A reply statement/evidence with respect to representation filed by SANKALP REHABILITATION TRUST was filed by the applicant/ agents for the applicant on **11/10/2023**.

g) A pre-grant hearing Notice was issued on 16/04/2024 and a hearing was fixed in the matter on**09/05/2024**.

h) A request for adjournment of hearing was filed by applicant on **06/05/2024.**

i) A pre-grant extended hearing Notice was issued on 13/05/2024 and a hearing was fixed in the matter on **12/06/2024**.

j) A request for adjournment of hearing was filed by opponenton**07/06/2024.**

k) A pre-grant extended hearing Notice was issued on 07/06/2024 and a hearing was fixed in the matter on **12/07/2024**.

l) A pre-grant extended hearing Notice was issued on 11/07/2024 and a hearing was fixed in the matter on **22/07/2024**.

m) A request for adjournment of hearing was filed by applicant on**19/07/2024.**

n) A pre-grant extended hearing Notice was issued on 29/07/2024 and a hearing was fixed in the matter on **24/09/2024**.

o) A request for adjournment of hearing was filed by opponent on **19/09/2024.**

p) A pre-grant extended hearing Notice was issued on 04/11/2024 and a hearing was fixed in the matter on **23/01/2025**.

q) A hearing (or written) submission with respect to hearing held on **23/01/2025**was filed byDr Deepak kumar,Dr. Shyam Ji Gupta on behalf of the Opponent, **SANKALP REHABILITATION TRUST** on **07/02/2025**.

o) A petition was filed by applicant's agent Devinder Singh Rawat to request for extension of time by one month, up to 07 March 2025, to file the written submission and relevant documents.

p) A hearing (or written) submission with respect to hearing held on **23/01/2025** was filed by ARCHANA SHANKER on behalf of the Applicant, **Merck Sharp & Dohme LLC**on **06/03/2025.**

5) <u>Grounds of opposition for a patent.</u>

Section 25(1) - Where an application for a patent has been published but a patent has not been granted, any person may, in writing, represent by way of opposition to the Controller against the grant of patent on the following ground—

(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—

(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: Provided that the ground specified in sub-clause (ii) shall not be available where such publication does not constitute an anticipation of the invention by virtue of sub-section (2) or subsection (3) of section 29;

(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;

(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;

(g) that the complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed;

(h) that the applicant has failed to disclose to the Controller the information required by section 8 or has furnished the information which in any material particular was false to his knowledge;

3).During the hearing the opponent restricted to only 3 grounds

a.Section 25(2)(e): Lack of inventive step

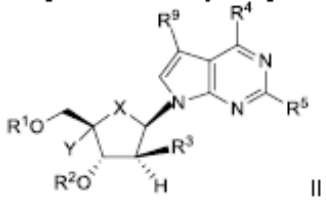
b. Section 25(2)(f): Invention is not patentable under section 3(d)

c. Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed

4) Claims as amended by the applicant and presented at commencement of the hearing :

1. A compound

or a pharmaceutically acceptable salt thereof, which has structural formula II:



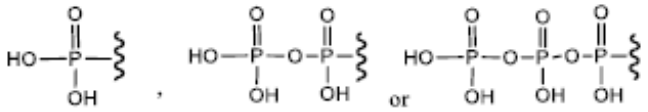
II

;

X is O;

Y is –C≡C-R^8;

R^1 is -H, -C(O)R^6, -C(O)OR^6, -C(O)N(R^6)$_2$,



or a pro-drug modification of the mono-, di- or triphosphate;

R^2 is -H, -C(O)R^{6a}, -C(O)OR^{6a} or -C(O)N(R^{6a})$_2$;

R^3 is –H;

R^4 is -N(R^X)$_2$, -NHC(O)OR^{6b},

-N(C(O)OR^{6b})$_2$, -NHC(O)N(R^{6b})$_2$, or -NHC(O)R^{6b};

R^5 is -H, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_3-C_7 cycloalkyl, halo,

-OR^X, -CN, -N(R^X)$_2$-NHC(O)OR^{6b}, -N(C(O)OR^{6b})$_2$, -NHC(O)N(R^{6b})$_2$, or -NHC(O)R^{6b};

R^6, **R^{6a}** and **R^{6b}** are each independently selected at each occurrence from -H, -C_1-C_6 alkyl,

or -C_1-C_6 haloalkyl;

R^8 is -H, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -C_3-C_7 cycloalkyl;

R^9 is -H, halo, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -CN, -OR^Y or -N(R^Y)$_2$;

R^X is independently selected at each occurrence from -H, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl,

aryl, or 5- or 6- membered monocyclic heteroaryl;

or when either or both of **R^4** or **R^5** is -N(R^X)$_2$, each R^X may optionally be joined together with

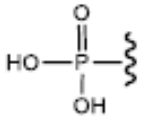
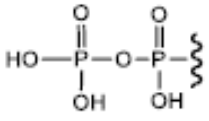
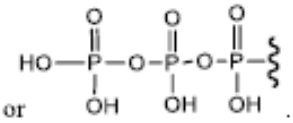
the nitrogen to which they are both attached to form a 5- or 6-membered monocyclic

heteroaryl or 9- or 10-membered bicyclic heteroaryl; and

R^Y is -H, -C_1-C_6 alkyl or -C_1-C_6 haloalkyl.

2. The compound as claimed in claim 1, or or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^1}$ is –H,


, 
or 
; and

$\mathbf{R^4}$ is -N(R^X)$_2$.

3. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^2}$ is -H.

4. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof wherein $\mathbf{R^4}$ is -N(R^X)$_2$.

5. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^5}$ is –H, halo, -C_1-C_6 alkyl, -OR^X, or -N(R^X)$_2$.

6. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^8}$ is–H.

7. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein $\mathbf{R^9}$ is –H, halo, -C_1-C_3 alkyl, -C_1-C_3 haloalkyl, -CN, -OR^Y or -N(R^Y)$_2$.

8. The compound as claimed in claim 1 to 7 or a pharmaceutically acceptable salt thereof, wherein

$\mathbf{R^X}$ is -H, -C_1-C_6 alkyl or -C_1-C_6 haloalkyl.

9. The compound as claimed in claim 1 or 2 or a pharmaceutically acceptable salt thereof, wherein:

$\mathbf{R^5}$ is –H, halo, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -CN, -OR^X, -N(R^X)$_2$, -NHC(O)OR^{6b}, -N(C(O)OR^{6b})$_2$, -NHC(O)N(R^{6b})$_2$, or -NHC(O)R^{6b}; and

$\mathbf{R^9}$ is –H, halo, -C_1-C_3 alkyl, -C_1-C_3 haloalkyl, -CN, -OR^Y or -N(R^Y)$_2$.

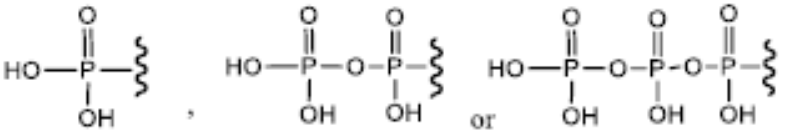
10. The compound as claimed in claim 9 or a pharmaceutically acceptable salt thereof wherein $\mathbf{R^4}$ is -N(R^X)$_2$.

11. The compound as claimed in claim 9 or a pharmaceutically acceptable salt thereof wherein **R1** is –H and **R4** is -N(R^X)$_2$.

12. The compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, wherein:

Y is –C≡CH;

R1 is -H, -C(O)R^6, -C(O)OR^6, -C(O)N(R^6)$_2$,



;

R2 is H, -C(O)R^{6a}, -C(O)OR^{6a} or -C(O)N(R^{6a})$_2$;

R3 is –H;

R4 is -N(R^X)$_2$, -NHC(O)OR^{6b} or -NHC(O)N(R^{6b})$_2$;

R5 is –H, halo, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, -CN, -OR^X or -N(R^X)$_2$;

R^6, **R^{6a}**, and **R^{6b}** are each independently selected at each occurrence from -H, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl;

R9 is –H, halo, -C_1-C_3 alkyl, -C_1-C_3 haloalkyl, -CN, -OR^Y, or -N(R^Y)$_2$;

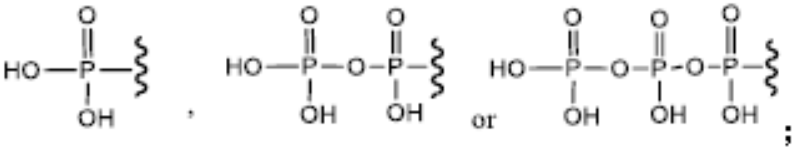
R^X is independently selected at each occurrence from -H, -C_1-C_6 alkyl, or -C_1-C_6 haloalkyl; and

R^Y is independently selected at each occurrence from -H, -C_1-C_6 alkyl or -C_1-C_6 haloalkyl.

13. The compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is -C≡CH;

R1 is -H,



;

R2 is H;

R3 is -H;

R4 is NH_2;

R5 is –H, halo or -NH_2; and

R9 is –H, halo or -CH3.

14. The compound as claimed in claims 1 or a pharmaceutically acceptable salt thereof, wherein one or more of R1, R2, R4 or R5 is selected as follows:

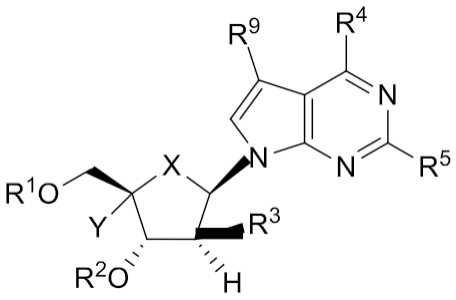
R1 is -C(O)R6, -C(O)OR6, -C(O)N(R6)2; and/or

R2 is -C(O)R6a, -C(O)OR6a or -C(O)N(R6a)2; and/or

R4 is -NHC(O)OR6b, -N(C(O)OR6b)2, -NHC(O)N(R6b)2, or -NHC(O)R6b; and/or

R5 is -NHC(O)OR6b, -N(C(O)OR6b)2, -NHC(O)N(R6b)2, or -NHC(O)R6b .

15. The compound as claimed in claim **1** or a pharmaceutically acceptable salt thereof, wherein the compound having structural Formula II,



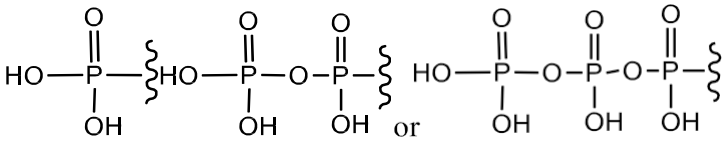
or a pharmaceutically acceptable salt thereof, wherein:

X is O;

Y is –C≡CH;

R1 is –H,

II,



,

; R2 is –H;

R3 is –H;

R4 is –NH2;

R5 is –H, halo or -NH2; and

R9 is –H, halo or –CH3.

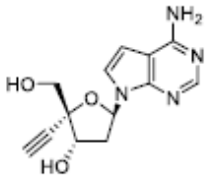
16. The compound as claimed in claim 1 that is:

1) 1)	2) (2R,3S,5R)-5-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2- (hydroxymethyl)tetrahydrofuran-3-ol ;
3) 2)	4) (2R,3S,5R)-5-(4-amino-5-fluoro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;

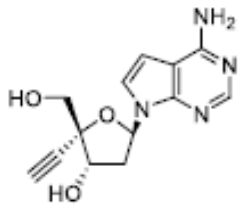
3)	(2*R*,3*S*,5*R*)-5-(4-amino-5-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
4)	(2*R*,3*S*,5*R*)-5-(4-amino-2-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
5)	(2*R*,3*S*,5*R*)-5-(4-amino-5-bromo-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
6)	(2*R*,3*S*,5*R*)-5-(4-amino-5-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
7)	(2*R*,3*S*,5*R*)-5-(4-amino-5-iodo-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
8)	(2*R*,3*S*,5*R*)-5-(2,4-diamino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
9)	(2*R*,3*S*,5*R*)-5-(4-amino-2-fluoro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol ;
10)	((2*R*,3*S*,5*R*)-5-(4-amino-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate;
11)	((2*R*,3*S*,5*R*)-5-(4-amino-5-fluoro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate;
12)	((2*R*,3*S*,5*R*)-5-(4-amino-5-methyl-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate;
13)	((2*R*,3*S*,5*R*)-5-(4-amino-2-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate;
14)	((2*R*,3*S*,5*R*)-5-(4-amino-5-chloro-7*H*-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl tetrahydrogen triphosphate;

or a pharmaceutically acceptable salt thereof

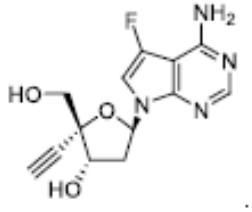
17. The compound as claimed in claim 1 that is:



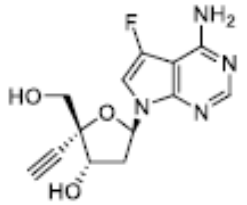
18. The compound as claimed in claim 1 that is a pharmaceutically acceptable salt of:



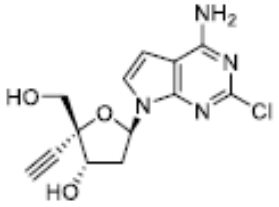
19. The compound as claimed in claim 1 that is:



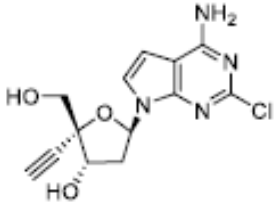
20. The compound as claimed in claim 1 that is a pharmaceutically acceptable salt of:



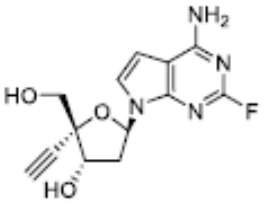
21. The compound as claimed in claim 1 that is:



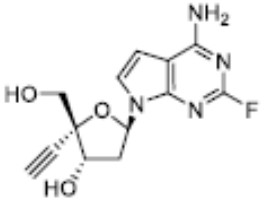
22. The compound as claimed in claim 1 that is a pharmaceutically acceptable salt of:



23. The compound as claimed in claim 1 that is:

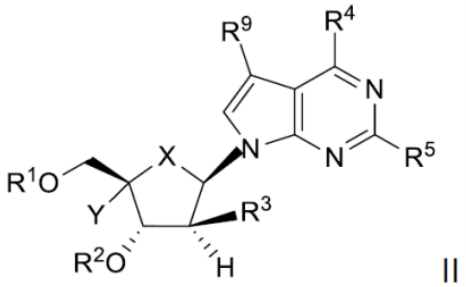


24. The compound as claimed in claim 1 that is a pharmaceutically acceptable salt of:



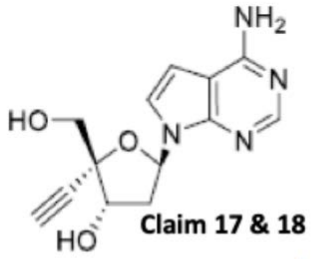
25. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and optionally comprising at least one anti-HIV agent selected from an HIV antiviral agent, an immunomodulator, and an anti-infective agent such as herein described.

5) As evident the pending claims are directed to the compounds of formula (I).

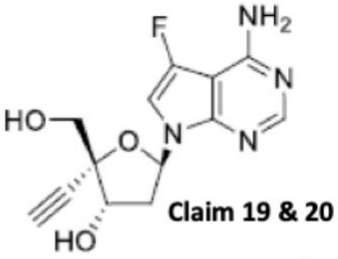


II

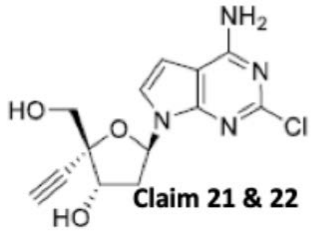
The specific compounds of the impugned invention are claimed in claim 16 to 24.



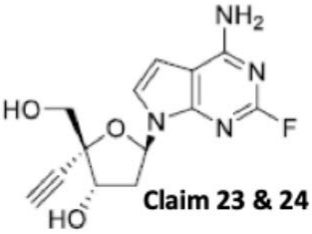
Claim 17 & 18



Claim 19 & 20



Claim 21 & 22

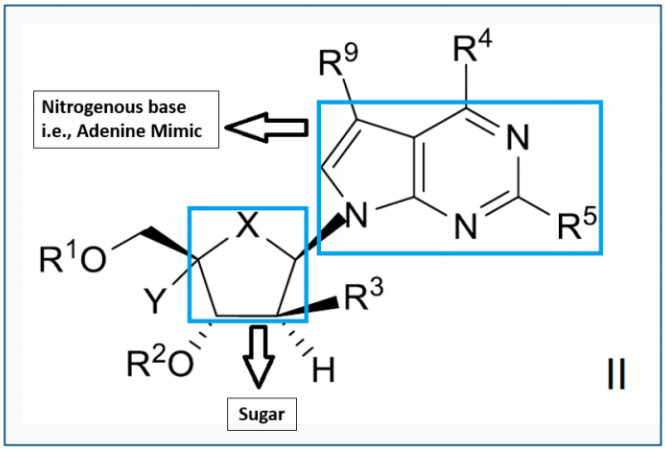


Claim 23 & 24

Presently claimed compounds have structure of Formula II having:

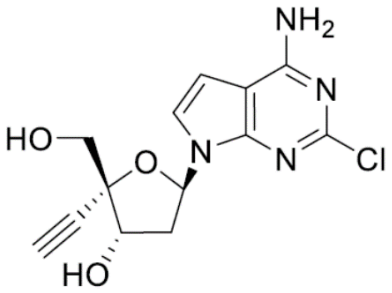
a. 4-substitued nucleoside derivatives which act as an adenine mimic with modified nitrogen at 6th position of the base.
b. 4’ position of nitrogenous base mimic is substituted with sugar moiety.

c. The sugar at 4th position (Y) is substituted with ethynyl group.



Formula II

One such compound that falls within the narrow scope of formula II has been designated number MK-8527 having the chemical structure:



6)Cited <u>Prior Art :</u>

Sr. No.	**7 Documents**	**8 Publication 9 Date**	**10**
D1	11 EP2177527A1 (WO2009009951A1)	12 2010	13 D1
D2	14 Kodama EI-Ichi et al., Antimicrobial Agents and 15 Chemotherapy, 2001, 45 (5), 1539-1546.	16 2001	17 D2
D3	**18 Hiroshi Ohrui., The Chemical Record, 2006, 6, 19 133–143.**	**20 2006**	**21 D3**
D4	22 Kristjan S. Gudmundsson et al., Nucleosides, 23 Nucleotides & Nucleic Acids, 2004, 23 (12), 1929– 24 1937	25 2013	26 D4
D5	27 Karen A. Kirby et al.,	29 2013	30 D5

	Antimicrobial Agents & 28 Chemotherapy 2013, 57(12), 6254-6264		
Annexure A	**31 Legraverend et al., Synthesis and Anti-HIV 32 Evaluation of 7-Deaza Analogues of Carbovir**	**33 1994**	**34 D6**
Annexure B	35 US2009/0274686A1	36 2009	37 D7
Annexure C	38 WO2002057425A2	39 2002	40 D8

The opponent submits that the presently claimed subject matter claimed in the impugned application lacks inventive steps in view of common general knowledge in art and combined with teachings of the following

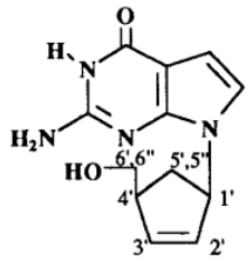
i. **D6**-Michel Legraverend , Anne-Marie Aubertin , Georges Obert , Christiane Huel & Emile Bisagni (1994) Synthesis and Anti-HIV Evaluation of 7-Deaza Analogues of Carbovir, Nucleosides and Nucleotides, 13:4, 915-923, DOI: 10.1080/15257779408011865. (This document was filed as additional document on 29th April 2024) (Annexure A)

ii. **D3**- Hiroshi Ohrui; 2′-Deoxy-4′-C-Ethynyl-2-Fluoroadenosine, a Nucleoside Reverse Transcriptase Inhibitor, Is Highly Potent Against All Human Immunodeficiency Viruses Type 1 and Has Low Toxicity; The Chemical Record, Vol. 6, 133–143 (2006

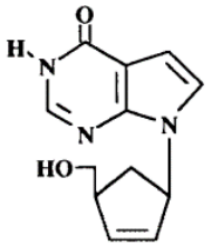
7)<u>D6 : MICHEL LEGRAVEREND ET AL:</u>

The Opponent submitted that the publication discloses the synthesis of analogs of Carbovir, which were evaluated for antiviral activity as shown below:

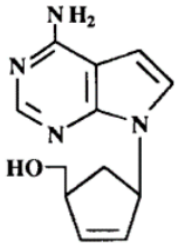
We have synthesized three new analogues of Carbovir as racemic mixtures, in which the 7-nitrogen atom of the purine ring has been deleted, providing 7-deaza guanine (**3**), 7-deazahypoxanthine (**4**) and 7-deazaadenine (**5**) analogues of Carbovir (**1**).



(3)



(4)



(5)

It is disclosed that Anti-HIV-1 and anti-HIV-2 activities have been observed with 7-deaza analogs 3 and 5 of Carbovir. **<u>Compound 5 was about ten times more potent than 3 against HIV- 1 and HIV-2 on different cell lines (Abstract)</u>**.

The document teaches that there are some critical differences between the Carbovir and compounds 3 to 5 wherein the sugar moiety of all compounds is the same whereas the “Base” moiety of Carbovir analogue compounds 3 to 5 possess some significant differences which are given below for ready reference.

41

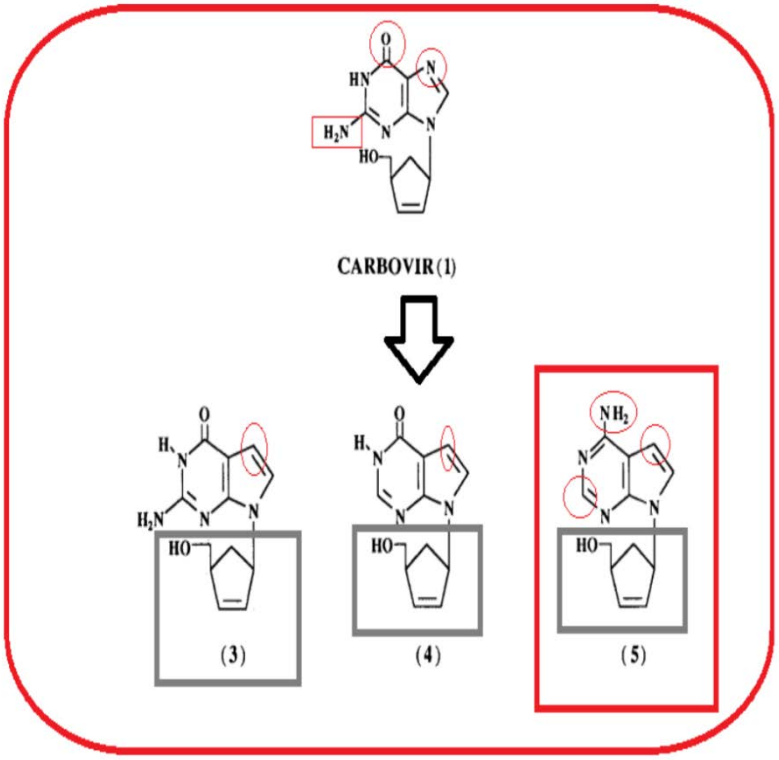


Figure 1

From figure 1 it is apparent that Legraverend teaches following points-

i. Absence of one “N” from five-membered ring.
ii. If “O” is present at 4th position of six-membered ring replace it with NH2
iii. If NH2 is present at 2nd position of six-membered ring remove the same.

Compound 5 possesses promising anti-viral activity (HIV-1 and HIV-2) after changing the nucleobase from Guanine to 7-deazaadenine. The document of Legraverend teaches that the nucleobase can be changed with 7-deazaadenine and that will provide significant activity. Legraverend et al. is related to synthesis and anti-HIV evaluation of 7-Deaza analogues of carbovir, which has emerged as the first carbocyclic nucleoside analogue with potential as a therapeutic agent for the treatment of AIDS1.

During the hearing, the Applicant contended that the Legraverend et al. document, published in 1994, is too old for a person skilled in the art to consider relevant. However, in response, the Opponent argued that document D4 (Gudmundsson et al.), which has been cited in the opposition, also references the same Legraverend document. This clearly indicates that despite its publication date, the document continues to be relevant in the field. A person skilled in the art does not disregard prior publications solely based on their age but rather assesses their technical relevance and applicability to the subject matter. Therefore, the Applicant’s argument that the Legraverend document is not considered due to its age is

unfounded, as its continued citation in later scientific literature proves its significance in the domain.

8) D3 <u>HIROSHI OHRUI ET AL;</u>

It is submitted that Hiroshi Ohrui et al disclose a compound (2′-Deoxy-4′-C-Ethynyl-2-Fluoroadenosine) that has exceptionally very high anti-HIV activity. It further discloses that this substance is highly potent against all HIV-1s and is expected to prevent the emergence of drug-resistant mutants, has low toxicity, and is stable to enzymatic catabolism.

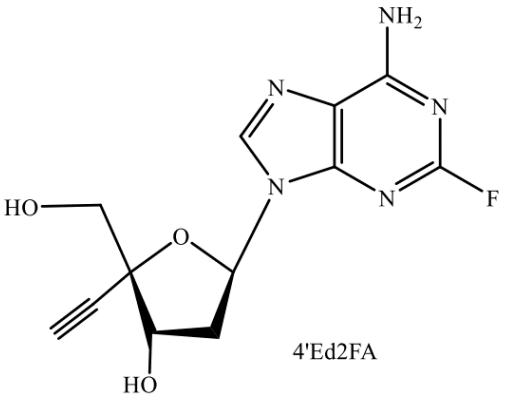
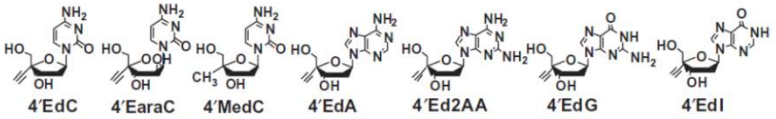


Figure 2: Structure of 2′-deoxy-4′-C-ethynyl-2-fluoroadenosine (4′Ed2FA)

D3 document pertains to the development of compound(s) that would purportedly prevent the emergence of drug-resistant mutants and also have low toxicity. It is disclosed that this resulted in the development of 2′-deoxy-4′-C-ethynyl-2-fluoroadenosine (4′Ed2FA) which was found to be highly potent against all HIV-1s, was stable to intracellular enzymatic catabolism and acidic degradation, and has a very long intracellular T1/2, does not greatly inhibit DNA polymerase γ, and does not have acute mouse toxicity. It is further disclosed that these results strongly suggest that 4′Ed2FA <u>deserves further study for the development of a highly potent therapeutic agent for HIV-1 infection</u> (AIDS), which may solve the problems of the existing HAART (internal page 142). The document in Table 4 further discloses various compounds and their anti-HIV activity which is reproduced below for ready reference.

Table 4. Anti-human immunodeficiency virus activity of selected 4′-*C*-substituted-2′-deoxynucleoside.



	EC_{50} (μM)[a]									
Compound	HXB2	KH65R	L74V	41/215	M184V	M184I	41/69/ 125/SG	MDR	Y181C	CC_{50} (μM)
4′EdC	0.0012	0.0008	0.0013	0.006	0.0024	0.0026	0.015	0.0012	0.0021	>200
4′EaraC	0.0071	0.015	0.026	0.026	0.71	0.48	0.17	0.0079	0.016	>200
4′MedC	0.0058	0.0071	0.0052	ND	0.2	0.74	ND	0.0033	ND	>200
4′EdA	0.008	0.0033	0.004	0.012	0.047	0.022	0.065	0.0062	0.011	>200
4′Ed2AA	0.0014	0.00035	0.0007	0.0017	0.0059	0.0027	0.0041	0.001	0.0008	>200
4′EdG	0.007	0.001	0.0012	0.019	0.008	0.0041	0.0068	0.0048	0.01	52
4′EdI	0.81	0.25	0.61	1.3	1.6	1.5	2.2	0.51	ND	>200
AZT	0.022	0.02	0.02	0.3	0.01	0.017	1.6	15.3	0.014	>100
3TC	0.71	ND	ND	ND	>100	>100	9.9	1.1	ND	>100
ddC	0.2	3.0	1.5	ND	2.2	ND	1.3	5.5	ND	>100
ddI	3.9	12.7	19.5	3.6	10.1	ND	12.2	25	ND	>100

[a]Anti-HIV activity was determined with MAGI assay.
EC_{50} = 50% effective concentration; CC_{50} = 50% cytotoxic concentration; AZT = 3′-azido-3′-deoxythymidine; ND = not determined.

Figure 3

Written arguments and discussion pursuant to the hearing attended on 23/01/2025 on behalf of the Opponent, SANKALP REHABILITATION TRUST, by applicant -MERCK SHARP & DOHME LLC on various grounds.

9) GROUND 1:LACK OF INVENTIVE STEP:

Opponent submits that the said impugned patent application may be rejected on the following grounds below, which are without prejudice and in the alternative to each other.

Section 25(2)(e): Lack of inventive step

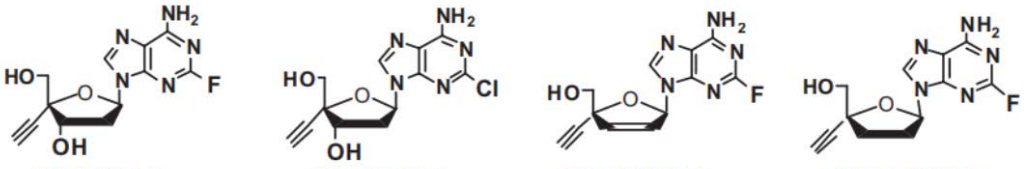
Section 25(2)(f): Invention is not patentable under section 3(d)

Section 25(2)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

The opponent submits that the presently claimed subject matter lacks inventive steps in view of common general knowledge in art and combined with teachings of the D6 and D3.The opponent submits that disclosures in the prior arts teach, suggest, and motivate a person skilled in the art to arrive at the invention claimed in the currently pending claims of the application. The Opponent submits that, as elaborated in the succeeding paragraphs, the present claimed subject matter lacks inventive steps given the documents cited in the pre-grant opposition matter. The Opponent submits that the present claimed subject matter is obvious given the disclosure of the cited prior arts and common knowledge available before the priority date of the impugned invention.Opponent, at the hearing, has retained only two documents, **namely**:a. **D3 (Hiroshi Ohrui., *The Chemical Record*, 2006, 6, 133–143) and Annex A (Legraverend et al., Synthesis and Anti-HIV Evaluation of 7-Deaza Analogues of Carbovir).**

The opponent submits that Table 4 of the document discloses a series of compounds that utilize different nucleoside bases while maintaining the same sugar moiety across all the compounds. This suggests that the invention explores variations in nucleoside bases as a means to achieve compounds with potentially optimized biological anti-viral activity. The data presented in Table 4 indicates that modifying the nucleoside base can influence the compound's properties, thereby demonstrating that the selection of an appropriate nucleoside base plays a critical role in enhancing the desired activity. This teaching reinforces the concept that structural modifications within the nucleoside base framework can lead to improved or optimized compounds while keeping the sugar moiety constant.Further, table 7 discloses the importance of halo-adenosines and shows the promising anti-HIV activity. The table disclosed the remarkable activity of 4'Ed2FA and 4'Ed2ClA against HIV-1 strains.

Table 7. Anti-human immunodeficiency virus activity of 4′-*C*-substituted-2′-deoxy-2-haloadenosines.



	Anti-HIV activity (MAGI assay, μg)		
Compound	HIV-1_{wild}	HIV-1_{MDR}	HIV-1_{M184V}
4′Ed2FA	0.00020	0.00014	0.0031
4′Ed2ClA	0.0019	0.0084	0.01
4′Ed42FA	0.80	0.15	1.8
4′Edd2FA	0.94	8.7	97
AZT	0.022	15.3	0.01
3TC	0.71	1.1	>100

MAGI = multinuclear activation of galactosidase indicator; HIV-1 = human immunodeficiency virus type 1; AZT = 3′-azido-3′-deoxythymidine; 3TC = 2′,3′-dideoxy-3′-thia-*L*-cyrtidine.

Figure 4

The opponent submits regarding the combination of D6 and D3:D6 it is evident the importance of 7-deazaadenine that reflect the promising anti-HIV activity. Therefore, a person skilled in the art would be motivated to use 7-deazaadenine as a promising nucleobase for the development of compounds that possess significant anti-HIV activity. D3 et al teaches the various compounds that also possess significant anti-HIV activity and they also showed promising activity against resistant strains. D3 disclose a compound 4'EdG that also possesses significant activity. The structure of that compound is given below.

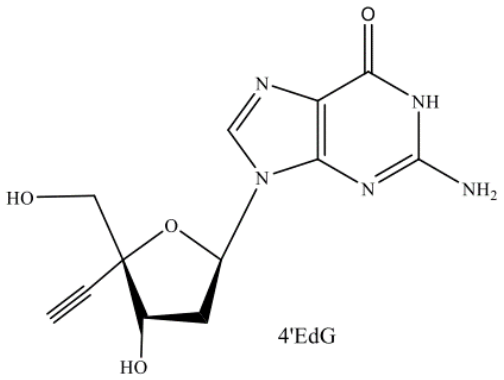


Figure 5

D6teach the absence of one “N” from five-membered ring, if “O” is present at 4th position of the six-membered ring replace it with NH2, if NH2 is present at 2nd position of the six-membered ring remove the same. The opponent submits that the combination of D6 and D3 leads to the compound that is claimed in claim 17 of the impugned application. The relevant structure given below clearly shows that the combination of both documents lead to the claimed subject matter.

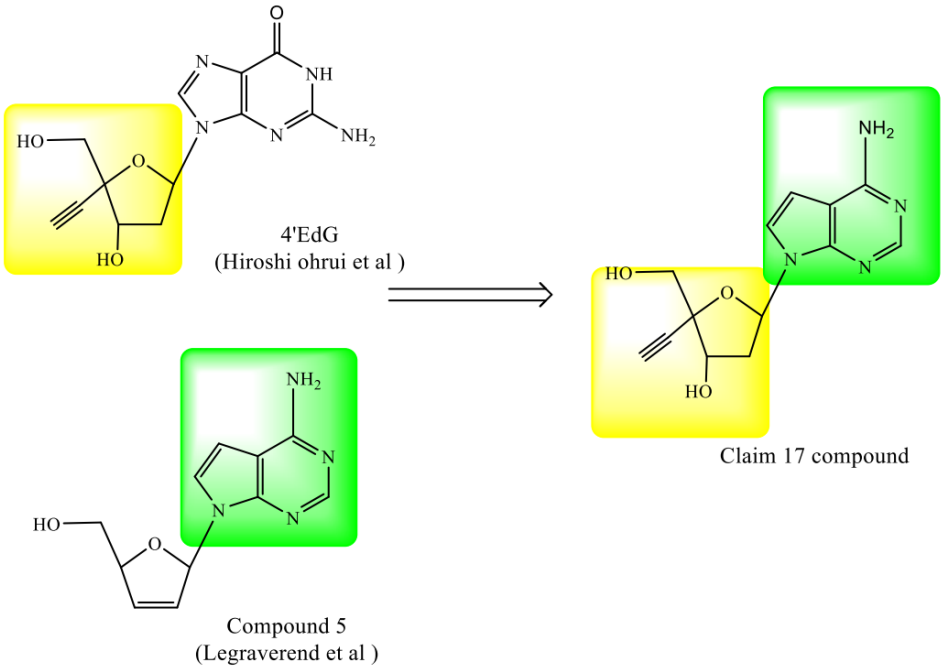


Figure 6

Figure 6 clearly shows that the claimed 17 compound is a mere combination of the teaching of two documents that are annexure A and D3.D3 disclose a compound 4’Ed2ClA which is given below.

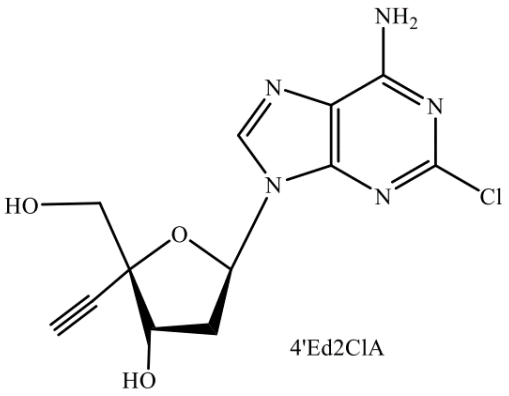


Figure 7

The opponent submits that the combination of teachings of annexure A and leads to the compound that is claimed in claims 21 and 22. The relevant structure is given below which clearly shows that the combination of both documents leads to the claimed subject matter.

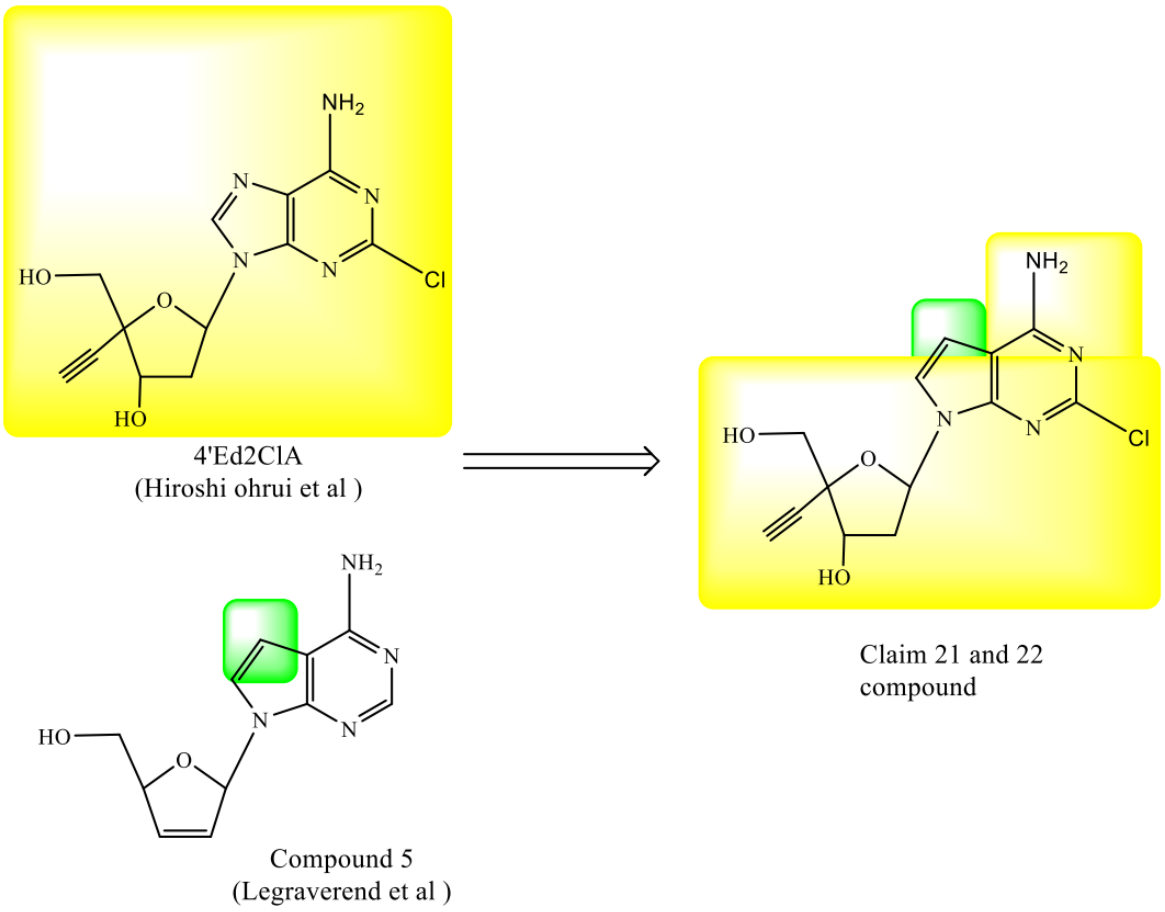


Figure 8

D6 teach that if nucleobase possesses amino group at 2nd position of six-membered ring remove the same. The compound 4'Ed2ClA doesn't have any amino group therefore, a person skilled in the art would keep Cl intact and doesn't replace it.Figure 8 clearly shows that the claimed

compounds 21 and 22 are a mere combination of the teaching of two documents that are annexure A and D3.Similarly,D3 further disclose a compound 4'Ed2FA which is given in Figure 2. The combination of teachings of D6 and D3 et al will leads to the compound that is claimed in claims 23 and 24. The relevant structure is given below which clearly shows that the combination of both documents leads to the claimed subject matter.

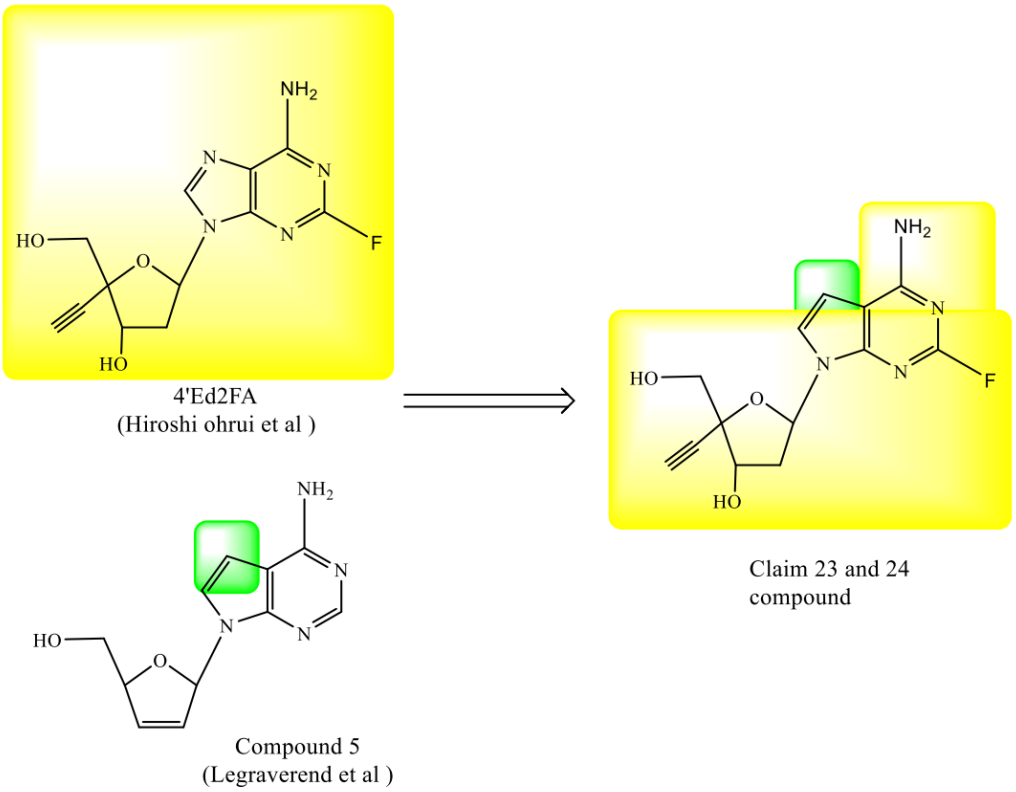


Figure 9

D6 teach that if nucleobase possesses amino group at 2nd position of the six-membered ring remove the same. The compound 4'Ed2FA doesn't have any amino group therefore, a person skilled in the art would keep F intact and doesn't replace it.Figure 9 clearly shows that the claimed compounds 23 and 24 are a mere combination of the teaching of two documents that are D6 and D3 .During the hearing, the Opponent argued that the alleged invention broadly claims aMarkush formula while also specifically claiming certain individual compounds that fall within this broader formula. The Opponent highlighted that Figures 6, 8, and 9 provide clear evidence that the compounds claimed in the impugned invention are derived by simply combining elements from two prior-art documents. This indicates that the claimed compounds are not the result of an inventive step but rather an obvious combination of known teachings. Since these specifically claimed compounds are encompassed within the broader Markush formula, the logical extension is that the entire Markush claim itself lacks inventiveness. If the individual compounds are rendered obvious by prior art, then the generalization of these compounds into a broader genus does not confer any additional inventive merit, thereby making the Markush formula as claimed in the impugned application equally obvious.

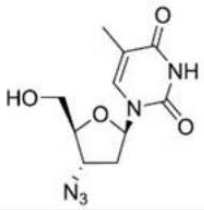
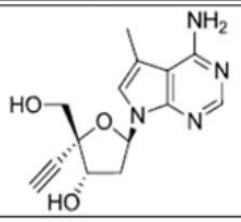
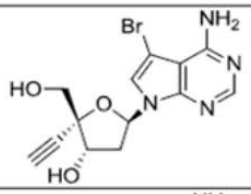
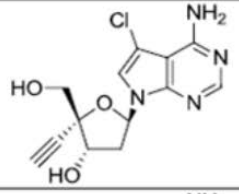
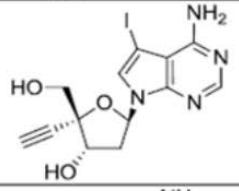
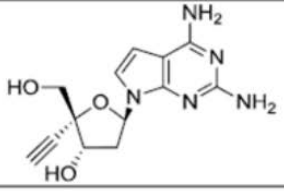
The opponent submits on ground of lack of technical advancement:

The Opponent relied on the affidavit of Dr. James filed by Applicant wherein Dr. James relied on a post-published document that disclosed a compound as MK-8527 (claimed in claims 21 and 22) that has a substantial technical advantage about off-target activity. During the hearing, the Opponent contended that the compound MK-8527 can be readily derived by combining the teachings of two prior art documents, namely Legraverend et al. and Hiroshi Ohrui et al. This demonstrates that the claimed compound does not involve an inventive step but rather results from an obvious combination of known elements. Furthermore, the Opponent argued that the property exhibited by MK-8527, as presented by Dr. James, is an inherent characteristic of the compound itself. Since this property naturally arises from the known structural framework of MK-8527, its discovery does not constitute a genuine technical advancement. Furthermore, merely identifying a pre-existing inherent property of a known or obvious compound does not qualify as an inventive contribution, as such properties would inevitably manifest when the compound is synthesized. Therefore, the subject matter of claims of instant application lacks any true technical advancement over the prior art.Furthermore, the affidavit fails to address the entire range of compounds claimed in the impugned specification. Instead, it focuses solely on a single compound, MK-8527, without providing any supporting evidence for the broader Markush formula. While the impugned specification encompasses a vast number of compounds, Dr. James's affidavit is limited to discussing the properties of MK-8527, making no assertion that the entire claimed range would exhibit the same technical advancements. In the absence of experimental data or reasoning demonstrating that all claimed compounds possess the alleged technical benefits, there is no basis to conclude that the broader Markush formula meets the requirements of inventive step. Consequently, the affidavit does not establish that the full scope of the claimed invention offers any genuine technical advancement. During the hearing, the Opponent submits that the affidavit itself acknowledges certain limitations in the claimed invention. Specifically, it discloses that:*"more than 600 compounds evaluated, only about 25 exhibited an IC50 <50 nM and adequate antiviral persistence." "structural modifications to the nucleoside core that were evaluated resulted in a greater than 1000-fold loss in antiviral potency"*. (affidavit para 28)

These statements indicate that even minor structural modifications to the nucleoside core can lead to a significant loss of antiviral potency. Furthermore, the affidavit reveals that the post-published data involved structural modifications that ultimately resulted in reduced potency. The Opponent also argued that none of these modifications were carried out following the teachings of the Legraverend document. This demonstrates that the claimed Markush formula, which covers millions of possible compounds, cannot be supported based on the performance of a single disclosed compound, MK-8527. The significant loss of potency upon structural variation suggests that technical advancement, if any, is restricted to MK-8527 alone and does not extend to the broader Markush claim. Therefore, relying on a single compound to justify the technical merit of an entire Markush formula is unwarranted, and the impugned invention fails to establish a uniform technical contribution across its claimed scope. The Opponent further submits that a single compound cannot justify the technical advancement of the entire range of the Markush formula. This is because the impugned specification itself includes various compounds that exhibit inferior activity compared to known compounds. Specifically, Table 3 of the impugned specification demonstrates that

several of the compounds are less effective than the standard compound, AZT. For instance, compounds 3, 5, 6, 7, and 8 all show inferior IC50 values when compared to AZT. This disclosure, present in the specification itself, undermines the assertion of a consistent technical advancement across the entire Markush formula, as it is evident that not all the compounds exhibit the desired properties. The relevant table is provided below for reference, further supporting the Opponent's argument that the range of compounds claimed is not uniformly superior.

TABLE 3

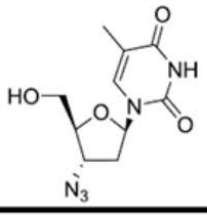
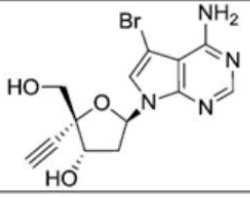
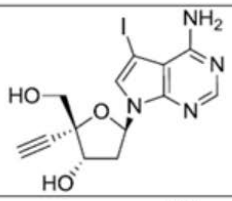
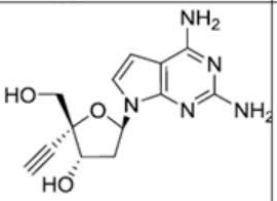
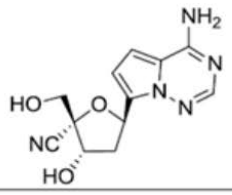
	Structure	Viking, IC_{50} (10%NHS)(nM)	CTG (µM)
AZT		37	>8.4
3		485	>8.4
5		209	>8.4
6		128	>8.4
7		1030	>8.4
8		194	>8.4

From the above, it is clear that several of the compounds disclosed in the impugned specification are inferior to AZT in terms of their antiviral activity, as evidenced by the data in Table 3. These inferior compounds are not only specifically disclosed in the specification but are also encompassed within the claimed Markush formula. This indicates that the impugned invention does not provide a consistent technical advancement over known compounds like AZT, as some

of the disclosed compounds fail to demonstrate superior activity. Therefore, the presence of these inferior compounds in the claimed range further supports the argument that the impugned invention lacks the technical advancement.

Similarly, Table 4 of the specification of instant application also suggests that there is no consistent technical advancement in the claimed Markush of the impugned specification. The relevant table is given below.

TABLE 4

	Structure	IC_{50} 24h (nM)	IC_{50} 72h (nM)	Fold shift IC_{50} 72h/24h
AZT		37	4713	127
5		22000	>42000	>1.9
7		17000	17000	1
8		840	29000	34.5
12		880	25000	28

Additionally, the Opponent submits that while the Applicant has filed an affidavit to demonstrate the superior activity of MK-8527 compared to islatravir, particularly in terms of better persistence value, the data provided in the affidavit itself reveals a different story. Specifically, the affidavit shows that islatravir has a lower IC50 value than MK-8527, as well as better persistence values in PBMCs. This contradictory data undermines the Applicant's claim of superior activity for MK-8527, as the results suggest that islatravir performs better in certain key aspects. The relevant extract from the affidavit is provided below for reference.

Compound	Cells	Virus	IC_{50} A (nM)	IC_{50} B (nM)	Persistence
ISL	MT4-GFP	WT	0.9 ± 0.6 (n=38)	19.6 ± 7.8 (n=8)	22
	PBMCs	WT-GFP	0.7 ± 0.3 (n=6)	42.5 ± 24.9 (n=8)	61
MK-8527	MT4-GFP	WT	7.2 ± 2.3 (n=11)	223.2 ± 103.8 (n=10)	31
	PBMCs	WT-GFP	1.2 ± 0.2 (n=7)	18.1 ± 4.8 (n=9)	15

The encircled values as shown above clearly show that MK-8527 showed inferior activity either in terms of IC50 value as well as persistence value.Additionally, the Opponent submits that during the hearing, the Applicant focused the discussion of technical advancement solely on MK-8527, without addressing the entire scope of the claim. This limited focus on just one compound fails to demonstrate that the entire range of compounds covered by the claim possesses the same technical advantages. As a result, the Applicant's argument does not substantiate a technical advancement across the full breadth of the claimed Markush formula.

The opponent submits on Lack of objective technical problem-solution approach:

It is respectfully submitted that the impugned patent application, as described in the background section of the specification, acknowledges a significant objective technical problem associated with using antiviral compounds to prevent HIV infection. The specification emphasizes that the continuous and widespread administration of such antiviral agents will inevitably lead to the emergence of new, resistant strains of the virus. This phenomenon of resistance development poses a serious concern in the long-term efficacy of antiviral therapies, necessitating novel approaches to overcome or mitigate this challenge. The relevant extract of the specification is reproduced here for ready reference.

While each of the foregoing drugs is effective in treating HIV infection and AIDS, there remains a need to develop additional HIV antiviral drugs including additional RT inhibitors. A particular problem is the development of mutant HIV strains that are resistant to the known inhibitors. The use of anti-retrovirals to treat AIDS often leads to viruses that are less sensitive to the inhibitors. This resistance is typically the result of mutations that occur in the reverse transcriptase segment of the pol gene. The continued use of antiviral compounds to prevent HIV infection will inevitably result in the emergence of new resistant strains of HIV. Accordingly, there is a continuing need for new RT inhibitors that are effective against mutant HIV strains.

During the hearing, the Opponent contended that the impugned specification fails to provide a solution to the objective technical problem as originally outlined in the specification itself. While the specification demonstrates RT polymerase activity, Viking assay/CTG, and antiviral persistence activity, it does not present any evidence of efficacy against resistant strains of the virus. The Applicant has not furnished any experimental data or conclusive findings to establish that the claimed invention effectively addresses or overcomes the problem of resistance

development in HIV strains.Furthermore, the Applicant has submitted the affidavit of Alexander James Bridges on 20th September 2024 in support of the present application. However, during the hearing, the Opponent contended that the affidavit filed by Dr. Bridges introduces an entirely new aspect of the invention, which was not originally disclosed in the specification. The Opponent argued that this amounts to an impermissible extension beyond the originally filed disclosure, potentially altering the scope of the invention as initially filed.

The Opponent submitted that in paragraphs 23 and 33 of his affidavits, Dr. James discussed the invention and stated that the compound in the present invention exhibits an in vitro off-target profile. The relevant excerpt is provided below for reference.

> 23. The novel compounds of the IN' 1899 application are Nucleoside Reverse Transcriptase Translocation Inhibitors (NRTTI), with a favorable *in vitro* off-target profile and PK characteristics suitable for long-acting oral dosing making some of them attractive potential clinical candidates for HIV Pre-Exposure Prophylaxis (PrEP). One of the compounds of the IN '1899 application, MK-8527, has been further developed and is currently being studied in several clinical trials for once-monthly administration for PrEP. It should be noted that for this particular indication, the people taking the drug are currently not sick in any way, so the safety margin for the drug has to be exceptionally good. This differentiates it from even rather similar compounds where even moderate toxicity in non-patients leads to an unacceptable profile for this indication, but not necessarily for treating HIV patients, who being infected are subject to a different cost-benefit analysis.
>
> 33. Thus, MK-8527 is a potent, novel NRTTI with a favorable in vitro off-target profile and the truly excellent, but unpredictable, PK characteristics suitable for long-acting oral dosing for treating HIV infection, which is now showing very favorable pharmacokinetics, and initial anti-HIV efficacy in human trials.

From the excerpts mentioned above, it is apparent that the Applicant has cast out an entirely new technical problem that was never stated in the as-filed specification.

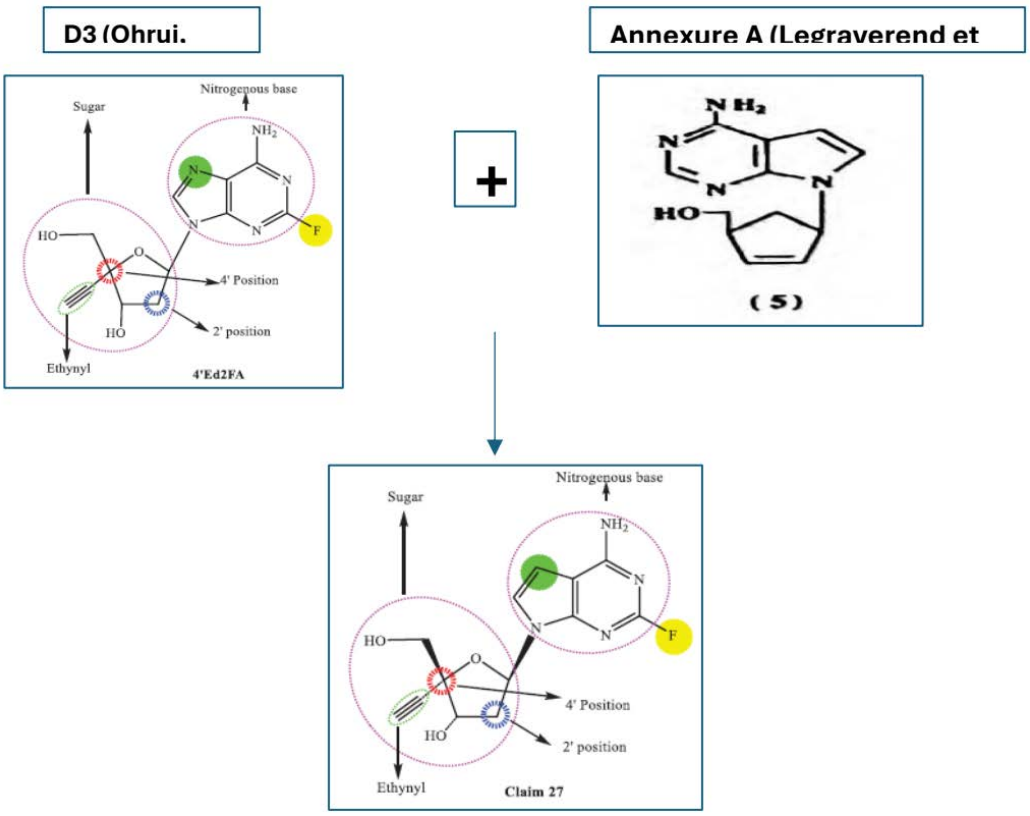
Additionally, the objective technical problem addressed by the invention was the need for inhibitors capable of effectively acting on mutant-resistant strains of viruses. However, a thorough review of the specification reveals that it does not provide any discussion or supporting evidence regarding the compound's activity against mutant strains. There is no experimental data, analysis, or any other information demonstrating that the present invention successfully addresses this objective problem or offers a viable solution.The opponent submits that from the above, it is apparent that the Applicant has cast a new problem and their solution which should not be allowed at this juncture.

In light of the above, it is submitted that the Applicant has not fulfilled the solution of the objective problem as it was cast in the specification.

During the hearing, the Opponent relied on case law (T 0415/11), which explicitly states that the inventive step must be demonstrated for the entire Markush range claimed in the specification. This case law reinforces the requirement that the technical advancement and inventive step must be proven across the entire scope of the claims, rather than being limited to a single compound. The relevant extract from the case law is reproduced here and is also attached as Annexure A for further reference.

> In view of decision T 939/92 it was a necessary prerequisite for the acknowledgement of an inventive step that what was claimed should not be arbitrary, but should achieve the technical effect required by the problem to be solved, an effect which should moreover be seen with substantially everything of the claimed subject matter, i.e. substantially all of the claimed subject-matter should be a solution to the underlying problem.

10) <u>APPLICANT'SSUBMISSION</u>:The applicant submits that



The applicant argues that the Opponent failed to apply the inventive step test as laid down in para. 118 **of the order of the Division bench of the Delhi High Court in Roche vs CIPLA**

(enclosed), RFA 92/2012[7], which states as follows:
To determine obviousness/lack of inventive step the following inquiries are required to be conducted.

Step No.1 To identify an ordinary person skilled in the art,

Step No.2 To identify the inventive concept embodied in the patent,

Step No.3 To impute to a normal skilled but unimaginative ordinary person skilled in the art what was common general knowledge in the art at the priority date.

Step No.4 To identify the differences, if any, between the matter cited and the alleged invention and ascertain whether the differences are ordinary application of law or involve various different steps requiring multiple, theoretical and practical applications,

Step No.5 To decide whether those differences, viewed in the knowledge of alleged invention, constituted steps which would have been obvious to the ordinary person skilled in the art and rule out a hindsight approach.

The applicant argues that structural similarity cannot form basis of selection of lead compound for obviousness and that biological activity of a molecule has to be seen as a whole.The applicant submits that Claimed invention is not obvious in view of cited prior art documents. The applicant submits that there is no motivation in D3 (**Hiroshi Ohrui et al**) for a person skilled in the art to modify the 'Adenosine' base to '7-deaza-adenosine' base. The applicant submits that Opponent in the hindsight manner has identified the prior D6 (**Legraverend et al.**,) merely because the moiety, '7-deaza-adenosine base' is present there. There is no coherent thread that combine the alleged prior art, i.e., teaching of one lead to second and so on. On the contrary, the Opponent, having knowledge of the claimed compound, thereafter in the hindsight manner has combine the prior art documents.D1, EP '527 teaches away from the ribose sugar of the claimed invention. D1 teaches to include 'fluorine' at 2-positon of the sugar moiety. There is no teaching, suggestion or motivation in the prior art to combine D3, D4 and D5 or D3, D1, and D5.

(a) The applicant also argues with respect to D3 that it teaches **away from using non-natural nucleobase.**The Applicant submits that Hiroshi Ohrui et al., discloses anti-HIV nucleoside that might prevent the emergence of drug-resistant HIV-1 mutants, must satisfy the following two conditions:

a) To prevent discrimination by HIV-1, the nucleoside must have a structure very much like those of dNs. Because the striking difference of the ddN and dN structures is whether they have 3'-OH, the nucleoside must have 3'-OH.

b) In spite of having 3'-OH, the nucleoside must be the chain terminator of RT-catalyzed biosynthesis of proviral DNA.

Based on the hypothesis, 4'-SdN (Fig. 2) was designed as a nucleoside that could satisfy the mentioned conditions: The **4′SdN** (4'-C-substituted-2′-deoxynucleoside) compounds was

designed as a nucleoside to solve the problem existing with **acquired immune deficiency syndrome chemotherapy** (highly active antiretroviral therapy) thereby **satisfying the structural requirements** as suggested on **page 134 and 135 of D3, Hiroshi Ohrui et al**.

a) It would be difficult for HIV-1 to discriminate 4'SdN from dN because 4'SdN has all the functional groups of dN.

b) The introduction of a substituent at the 4'-position makes the 3'-OH into a very unreactive neopentyl-type secondary alcohol. Thus, the 3'-OH of 4'SdN will be used for HIV to mistake 4'SdN for dN, but is too unreactive to be used for the elongation of proviral DNA by RT. Therefore, 4'SdN could be the chain terminators of proviral DNA biosynthesis.

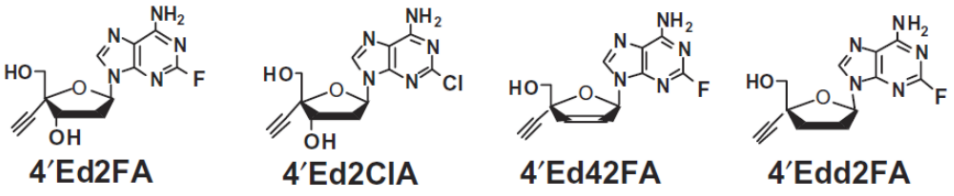
c) Steric hindrance between 3'-OH and 4'-substituent changes the conformation of the furanose ring of 4'SdN preferably to the 3'-endo conformation (N-type). This results in 4'SdN being less susceptible to both acidic and enzymatic degradation than that of dN and ddN.

d) Further, the electron-withdrawing 3'-OH makes 4'-SdN more acid stable than does ddN even with purines. Thus, various purine derivatives can be made in this way.

e) The lipophilic substituent at the 4'-position imparts more lipophilicity to 4'SdNs, thus enabling them to penetrate the cell membrane efficiently. This may possibly enhance their bioavailability.

Thus, the direction of teaching in D3 is towards not to change the natural nucleobase (adenine and guanine) core ring structure and instead make modification at the sugar moiety. Table 7, list the compounds disclosed in D3, Hiroshi Obrui et al.

Table 7. Anti-human immunodeficiency virus activity of 4′-*C*-substituted-2′-deoxy-2-haloadenosines.



Compound	Anti-HIV activity (MAGI assay, μg)		
	$HIV\text{-}1_{wild}$	$HIV\text{-}1_{MDR}$	$HIV\text{-}1_{M184V}$
4′Ed2FA	0.00020	0.00014	0.0031
4′Ed2ClA	0.0019	0.0084	0.01
4′Ed42FA	0.80	0.15	1.8
4′Edd2FA	0.94	8.7	97
AZT	0.022	15.3	0.01
3TC	0.71	1.1	>100

MAGI = multinuclear activation of galactosidase indicator; HIV-1 = human immunodeficiency virus type 1; AZT = 3′-azido-3′-deoxythymidine; 3TC = 2′,3′-dideoxy-3′-thia-*L*-cyrtidine.

4’EdA – No substitution at 2-position of Adenine ring

4’EDAA – Amino at 2-position of Adenine ring

4’Ed2FA – Fluorine at 2-position of Adenine ring (Islatravir)

4’Ed2ClA - Chlorine at 2-position of Adenine ring

Further, the opponent argued that D3 contains the most relevant compound, Islatravir, which allegedly provided the applicant with the motivation to derive the compounds of the present invention by modifying a halogen.The Applicant humbly submits that the Opponent in the hindsight manner has identified the prior art and thereafter particularly select a portion of the compound. In that process, the Opponent has ignored the other part of the molecule. There is no motivation in D3 for a person skilled in the art to modify the ‘Adenosine’ base to ‘7-deaza-adenosine’ base.Further, the applicant submits a comparative assay analysis of Islatravir and MK-8527 supported by Dr Bridges Affidavit (Page 15, Para 32) wherein, at similar doses:

a) **MK-8527** shows superior persistence in human PBMCs after washout, with active drug levels:

a. **40-fold higher** than plasma concentrations at 72 hours.

b. **80-fold higher** at 168 hours.

b) MK-8527 maintains better antiviral activity and safety in **CD4+ T-cells**.

c) MK-8527 has **longer retention** and effectiveness than Islatravir, making it a more promising HIV treatment.

d) **Islatravir** had previously been shelved following an observed lymphocyte depletion at the administered dose in human trials.

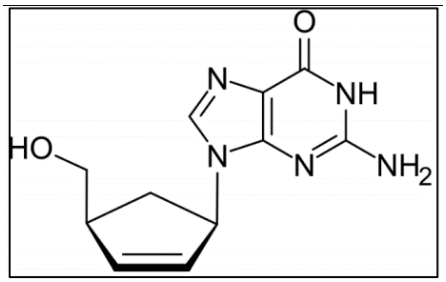
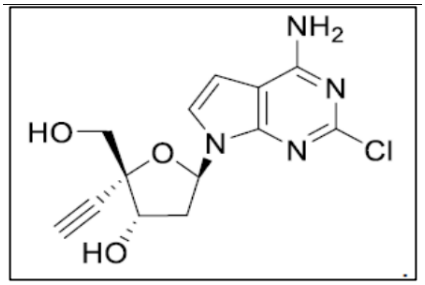
Compound	Cells	Virus	IC_{50} A (nM)	IC_{50} B (nM)	Persistence
ISL	MT4-GFP	WT	0.9 ± 0.6 (n=38)	19.6 ± 7.8 (n=8)	22
	PBMCs	WT-GFP	0.7 ± 0.3 (n=6)	42.5 ± 24.9 (n=8)	61
MK-8527	MT4-GFP	WT	7.2 ± 2.3 (n=11)	223.2 ± 103.8 (n=10)	31
	PBMCs	WT-GFP	1.2 ± 0.2 (n=7)	18.1 ± 4.8 (n=9)	15

As such, MK-8527 represents a substantial and non-obvious advance over the allegedly closest compound in the art.

(b) POSA would not select 7-Deaza nucleobase from Ann.-A (Legraverend et al.)

Legraverend et al. is related to synthesis and anti-HIV evaluation of 7-Deaza analogues of **carbovir, which is structurally distinct** from the compound of IN '899.

At the outset, Legraverend et al., is old document, published in 1994 and the research has moved forward. The Applicant humbly submits that virology is very fast changing field of biological science. Viruses mutate very fast and new one arises which are resistant to known drugs. For instance, the recent pandemic of COVID-19, the SARS virus was known much before the year 2019. However, the drugs known as of 2019 were ineffective against COVID-19. Legraverend et al. is related to synthesis and anti-HIV evaluation of 7-Deaza analogues of c**arbovir, which has emerged as the first carbocyclic nucleoside analogue with potential as a therapeutic agent for the treatment of AIDS1 and is structurally distinct from the compounds of IN '899**, including exemplary compound MK-8527.

Carbovir	**MK-8527**
	

The structural differences between the compounds are notable: the nitrogenous bases are distinct, **with carbovir containing guanine and adenine, whereas MK-8527 focuses on an adenine base with a substituted sugar moiety** featuring an ethynyl group. Additionally, carbovir lacks any halogen substitution, whereas MK-8527 incorporates specific structural modifications that set it apart. Furthermore, there is no compound in D7 that features a sugar moiety substituted with an ethynyl group. This significant structural difference further distinguishes the compounds in D7 from MK-8527, highlighting the uniqueness of the latter's design.

(c) Hiroshi Ohrui et al. (D3) in view of Legraverend et al., (D6)

There is no motivation to combine D3 and D6 to arrive at the compounds of our invention, given their significant structural differences. D3 features Islatravir, which has a non-modified nucleoside base with a fluorine substitution, while D6 presents compounds with a 7-deazadenine base and a non-modified sugar moiety.In contrast, IN '899 incorporates a modified sugar moiety to enhance efficacy and reduce toxicity, which is not suggested by either reference.Opponent in the hindsight manner has identified the prior art D6 (Legraverend et al) merely because the moiety, '7-deaza-adenosine base' is present there., but the opponent has ignored the fact that the asserted prior art compound must be analysed in terms of its chemical structure as a whole. In this regard, reference has been made to the case law(**Merck vs Glenmark (enclosed), order of Delhi High Court**) by the applicant that held that the biological activity of a molecule is dependent on its structure as a whole .

(d)POSA would not consider Carbovir as a lead compound (Legraverend et al et al.)

The Applicant submits that at the priority date (28th March 2014) of the instant application, a person skilled in the art would not consider Carbovir, disclosed in Legraverend et al et al, 1994 as the starting point.The applicant submits that It is submitted that Legraverend et al. is a 1994 document and there is a gap of 20 years between the present invention and Legraverend et al. Therefore, a person skilled in art would not select carbovir as a lead compound from Legraverend et al. Legraverend et al., being a 1994 document, is now outdated given the significant advances and mutations that have occurred since then. The vast time gap between its publication and the current state of research renders it largely irrelevant and not useful for the present context. The considerable progress in the field over the years makes this document of limited value for assessing the current invention. The applicant submits that Carbovir was selected by the Opponent in hindsight only after having knowledge of the present invention of the Applicant. The applicant does not claim to have synthesized deazadenosine itself. Rather, what is claimed is a series of compounds having a unique arrangement of a modified sugar moiety with a base, designed to lower toxicity while enhancing targeted activity. This contrasts with the compound Islatravir, alleged by the Opponent as the closest compound in D3, which failed at particular doses in humans to achieve a desired therapeutic balance of efficacy and reduced toxicity. The applicant's invention addresses these shortcomings, offering a more promising approach.The applicant further gives submission for other possible combinations of prior art which are not being repeated for sake of brevity and also as opponent restricted to combination of D6 and D3

The applicant states that Prior art directed towards modifying the sugar moiety:cited prior art documents predominantly focused on modifying the sugar moiety to enhance drug stability, metabolism, and efficacy. The teaching of the prior art documents at the time of the present invention is in the direction that not to perturb the nucleobase and instead modify the sugar moiety. Therefore, a person skilled in the art, at the priority date of the instant application would have been inclined to modify the sugar moiety in order to develop novel HIV inhibitors.The inventor(s) of the present application marks a significant shift from the teaching of the prior art documents and instead make modification to both the nucleoside base and the sugar moiety. This dual modification strategy aims to achieve superior selectivity, stability, and viral inhibition, offering a more effective therapeutic outcome than previously taught methods.

11) DISCUSSION AND CONCLUSION GROUND 1:LACK OF INVENTIVE STEP:

: On analysis of the arguments of both the parties it is found that D3 features Islatravir, which includes a non-modified nucleoside base with a fluorine substitution, while D6 presents compounds with a 7-deazadenine base and a modified sugar moiety to "2′,3'-dideoxy-2′,3'-didehydro-cyclopentene. These significant structural differences particularly in the nucleosidic base and sugar modifications create two entirely distinct approaches with no logical basis for combining them. D6 deals with the synthesis and evaluation of 7-deaza analogues of carbovir, which is structurally distinct from the compounds of IN '899, including MK-8527. Therefore, D6 does not provide any motivation or basis to combine its teachings with D3 to achieve the claimed invention. Based on the submissions by the

applicant ,there is also no coherent thread that combine the alleged prior art, i.e., teaching of one lead to second and so on.The teaching of the prior art documents, at the time of priority of the instant application, is to modify the sugar moiety and retain the core base unmodified. Although, there is teaching to make substitution on the nucleobase. However, there is no teaching, suggestion or motivation to change the base structure. In fact, the approach was to retain the core structure of nucleobase while modifying the sugar ring so as to mimic like a natural nucleobase.There is no direction, for a person skilled in the art to combine D3, and D6 to arrive at claimed compounds. The structural and functional differences between the references make any combination improbable without the benefit of prior knowledge of the claimed invention.The subject matter of amended claims is non obvious over the cited prior art and are therefore considered inventive u/s (1)(ja) of Patents Act 1970.

12). <u>GROUND II – PATENTABILITY UNDER SECTION 3(d)</u>

OPPONENT'S SUBMISSION :The Opponent states that the compounds claimed in the impugned patent application are a derivative of the known compound 4'Ed2FA and that the Applicant failed to provide the enhanced efficacy data in the specification.The Opponent submits that while the Applicant has filed an affidavit to demonstrate the superior activity of MK-8527 compared to islatravir, particularly in terms of better persistence value, the data provided in the affidavit itself reveals a different story. Specifically, the affidavit shows that islatravir has a lower IC50 value than MK-8527, as well as better persistence values in PBMCs. This contradictory data undermines the Applicant's claim of superior activity for MK-8527, as the results suggest that islatravir performs better in certain key aspects. The relevant extract from the affidavit is provided below for reference.

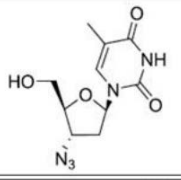
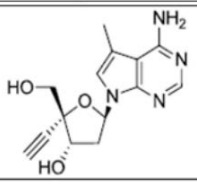
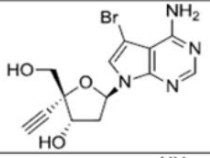
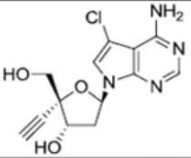
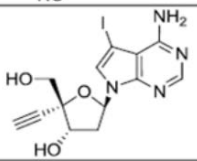
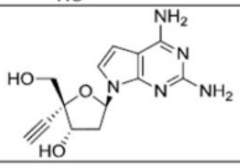
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The encircled values as shown above clearly show that MK-8527 showed inferior activity either in terms of IC50 value as well as persistence value.

Additionally, the Opponent submits that a single compound cannot justify the requirement of enhanced efficacy for the entire range of the Markush formula. This is because the impugned specification itself includes various compounds that demonstrate inferior activity when compared to known compounds. Specifically, Table 3 of the impugned specification shows that several of the compounds are less active than the standard compound, AZT. For example, compounds 3, 5, 6, 7, and 8 exhibit higher IC50 values compared to AZT, indicating inferior antiviral potency. This data, which is provided directly in the impugned specification,

undermines the claim of enhanced efficacy across the entire range of the Markush formula. The relevant table is provided below for reference, highlighting the inferior performance of these specific compounds.

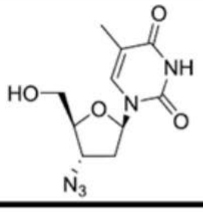
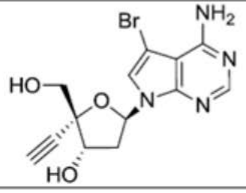
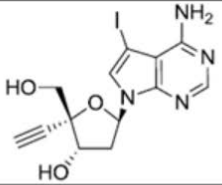
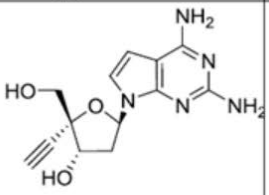
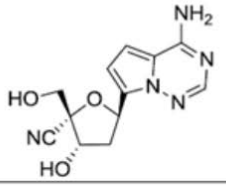
TABLE 3

	Structure	Viking, IC_{50} (10%NHS)(nM)	CTG (µM)
AZT		37	>8.4
3		485	>8.4
5		209	>8.4
6		128	>8.4
7		1030	>8.4
8		194	>8.4

From the above, it is evident that several compounds disclosed in the impugned specification exhibit inferior activity compared to AZT. These compounds are not only explicitly mentioned in the specification but are also encompassed within the broader Markush formula claimed in the application. This demonstrates that the claimed invention does not consistently provide enhanced efficacy over the known compound, AZT. Since multiple compounds within the claimed scope fail to show enhanced efficacy, the alleged technical advancement does not apply uniformly across the entire range. Therefore, the impugned invention lacks the requirement of enhanced efficacy in comparison to AZT.

Similarly, table 4 of the impugned specification also suggests that there is no enhanced efficacy in the claimed Markush of the impugned specification. The relevant table is given below.

TABLE 4

	Structure	IC_{50} 24h (nM)	IC_{50} 72h (nM)	Fold shift IC_{50} 72h/24h
AZT		37	4713	127
5		22000	>42000	>1.9
7		17000	17000	1
8		840	29000	34.5
12		880	25000	28

In light of the above, it is evident that the presently claimed subject matter lacks enhanced efficacy data. Thus, the claimed invention falls squarely within the ambit of section 3(d) and ought to be rejected.

13) APPLICANT SUBMISSSION ON GROUND II PATENTABILITY SECTION 3 (d)Applicant submits that the instant application is directed to new chemical entities including MK-8527, and are not attracted by section 3(d) of Patents Act 1970.The applicant refers to the Division Bench of the Hon'ble Delhi High Court in ***Roche vs Cipla, RFA 92/2012*** did not hold Erlotinib, the claimed invention as being a derivative of a prior art compound even when there was a high structural similarity. The court dealt with this issue under "INVENTIVE STEP" and NOT Section 3(d) and treated Erlotinib as a New Chemical entity.The applicant continues to submit that the instant subject matter of claims is better off than the Roche Vs. CIPLA case, as the molecule is significantly different from any of the prior art compounds. The compounds of the present invention IN'1899 were evaluated using a variety of assays, each designed for specific purposes as detailed below.

- HIV-1 RT Polymerase Assay: This assay tests a compound's ability to inhibit HIV reverse transcriptase (RT), which is key for viral replication. The assay combines RT with the compound (in its active triphosphate form) or DMSO to assess inhibition. (Refer: Page 103)
- Viking Assay: The **Viking Assay** typically tests a drug's **ability to inhibit HIV replication** in a cell-based system, **where the virus is actively replicating**. (Refer: Page 105)
- CTG Assay (Cell Titer-Glo Luminescent Cell Viability Assay): It often involves measuring the **cytotoxicity** and its **antiviral potency and CTG helps in Assessing cytotoxicity and cell viability in CellTiter-Glo Luminescent Cell Viability Assay (CTG)**. (Refer: Page 106)
- Antiviral Persistence Assay: This assay tests how long the drug remains effective after it has been removed from the system (washed out of the cells). If a compound has **long-lasting antiviral activity after washout**. It also helps us understand **how well the drug penetrates and persists in the target cells,** like PBMCs (immune cells). (Refer: Page 108)

- Adenosine Deaminase (ADA) Half Life Assay: **Adenosine Deaminase (ADA)** is an enzyme that breaks down adenosine, which could interfere with the drug's effectiveness if the compound is a substrate for ADA. If the compound is **resistant to ADA**, it can **stay active longer** in the body, which is a desirable property, especially for drugs targeting **immune cells** (like **CD4+ T-cells**). This test helps determine the **stability** of the drug in the presence of ADA, reducing the risk of **premature degradation**. (Refer: Page 112)

  Even otherwise, the applicant has provided EC50, CC50 and IC50 values of compounds of in the patent specification also discussed above. The Applicant has provided **comparative data with respect to similar doses of islatravir by way of affidavit of Dr. Alexander Bridges and post-published article** in respect of the present application. The table is not re-produced for sake of brevity.

14)DISCUSSION AND CONCLUSION ON THE GROUND II PATENTABILITY SECTION 3 (d):

D3 and D6 does not identify any compound similar to claimed in the present application.After going through D3 and D6 it is observed that it does not exemplify any**4-substituted nucleoside derivatives** that can be used for the treatment and prophylaxis of viral infections effective against mutant HIV strains and are intended as HIV reverse transcriptase inhibitors as anti-HIV/AIDS. As such, MK-8527 represents a substantial and non-obvious advance over the allegedly closest compound in the art.Page 30 onwards of the specification clearly provides several examples including synthesis of each along with MK-8527 (Example 4, Page 48).It is observed that compounds of invention IN'1899 behave as NRTTIs (Nucleoside Reverse Transcriptase Translocation Inhibitors) and considering the affidavit NRTTIs are effective because they strongly block HIV replication where they can then either immobilize the RT enzyme at that position, so it cannot move to the next nucleobase to continue DNA chain extension and the NRTTI mechanism has the advantage that it also sequesters the RT enzyme on a defective DNA strand, thus permanently inhibiting it making the compounds particularly good at this inhibition.MK-8527, it is a good substrate for adenosine kinase and is converted

into an active triphosphate ester form. Once activated, MK-8527 can inhibit HIV RT. Although the drug's triphosphate form has limited membrane permeability, it remains inside cells, providing a long half-life. MK-8527 meets the required efficacy and toxicity criteria better than other reverse transcriptase. With an IC50 of 3.4 nM in human PBMCs, it demonstrates strong antiviral activity and prolonged efficacy, while remaining selective in enzyme assays. MK-8527-TP demonstrates excellent pharmacokinetics with high oral absorption (100% in rhesus monkeys) and a long intracellular half-life of ~48 hours in PBMCs, much longer than the parent compound's plasma half-life (~7 hours). Active drug levels in PBMCs are significantly higher than in plasma, peaking at 80-fold higher at 168 hours. Clinical data confirms a terminal plasma half-life of at least 9 days, ensuring prolonged antiviral activity.

The comparative data have been provided, assay analysis of Islatravir and MK-8527, supported by Dr Bridges Affidavit (Page 15, Para 32) wherein, at similar doses:

a**)MK-8527** shows superior persistence in human PBMCs after washout, with active drug levels:i.) **40-fold higher** than plasma concentrations at 72 hours. ii). **80-fold higher** at 168 hours.b) MK-8527 maintains better antiviral activity and safety in **CD4+ T-cells**.c). MK-8527 has **longer retention** and effectiveness than Islatravir, making it a more promising HIV treatment.d) **Islatravir** had previously been shelved following an observed lymphocyte depletion at the administered dose in human trials.

The claimed compounds have distinguishable features in its chemical structures and shows unexpectedly remarkable antiviral activity against HIV. Therefore, the claimed compound is not a mere analogue and hence does not fall within the ambit of section 3(d).

15)<u>GROUND-III: INSUFFICIENT DESCRIPTION [25(1)(g)]</u>

OPPONENT'S SUBMISSION The opponent submits that complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed. They submit that it is a well-settled law that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue effort. Further, the opponent states that claims of impugned application are not fairly based on the specification and the complete specification does not fairly describe the invention and the method by which it is to be performed. The opponent states that as described in the background section of the specification, acknowledges a significant objective technical problem associated with using antiviral compounds to prevent HIV infection. The specification emphasizes that the continuous and widespread administration of such antiviral agents will inevitably lead to the emergence of new, resistant strains of the virus. This phenomenon of resistance development poses a serious concern in the long-term efficacy of antiviral therapies, necessitating novel approaches to overcome or mitigate this challenge. The relevant extract of the specification is reproduced here for ready reference.

While each of the foregoing drugs is effective in treating HIV infection and AIDS, there remains a need to develop additional HIV antiviral drugs including additional RT inhibitors. A particular problem is the development of mutant HIV strains that are resistant to the known inhibitors. The use of anti-retrovirals to treat AIDS often leads to viruses that are less sensitive to the inhibitors. This resistance is typically the result of mutations that occur in the reverse transcriptase segment of the pol gene. The continued use of antiviral compounds to prevent HIV infection will inevitably result in the emergence of new resistant strains of HIV. Accordingly, there is a continuing need for new RT inhibitors that are effective against mutant HIV strains.

But, the specification failed to provide such data that reflects that the compound in instant application is effective against the resistant strains of HIV. The opponent submits that the claimed subject matter asserts improved activity wherein the Applicant claims millions of compounds, but the specification only discloses experimental data for a few compounds. The absence of data or representative examples for other compounds within the broad Markush formula raises serious concerns about whether the alleged advantage applies to the entire claimed scope. Without sufficient disclosure, a skilled person cannot reasonably predict whether all covered compounds would achieve the same technical effect, making the disclosure insufficient. The opponent further submits that a patent specification must provide clear and sufficient guidance to enable a skilled person to reproduce the invention without undue experimentation. In the present case, the lack of multiple working examples or predictive structure-activity relationships means that a skilled person would need to undertake an undue burden of research and experimentation to determine which compounds within the broad Markush structure are effective. This deficiency further highlights the insufficiency of the disclosure.For an invention to be patentable, it must be fully and sufficiently disclosed so that a person skilled in the art can carry it out. However, in this case, the Applicant has claimed an expansive genus of compounds while disclosing a handful of working examples. This approach does not satisfy the legal requirements for sufficiency, as it fails to provide reasonable assurance that the claimed invention is applicable across its entire scope.

16) APPLICANT'S SUBMISSION :GROUND III – LACK OF SUFFICIENCY The Applicant submits that the claims and specification of the present application have been sufficiently disclosed in the patent specification. The Opponent at the hearing attempted to mislead that the claims of the present application are not sufficiently described. The Opponent at the hearing made the arguments without any reasoning wherein the Opponent seems to suggest that the compounds are speculative and in the absence of examples.

Referring to FDC Ltd vs Sanjeev Khandelwal and Ors15 (2014 SCC OnLine IPAB 23) 114. *As per section 10(4) every complete specification shall fully and particularly describe the invention and disclose the best method of performing the invention which is known to the applicant. However, it is not mandatory that the claims should be representative of the best method. The Controller suggested amendment in claim 13 only for clarity purpose i.e. for bringing claim 13 in line with the claim 1. The clarity issue cannot be correlated to insufficiency of description. (Emphasis added*)

Tata Global beverages Limited vs. Hindustan Unilever Limited16 (2012 SCC OnLine IPAB 162 : [2012] IPAB 164)….*The claims represent generalisations of the examples and have to be read in a broad, technically meaningful way, but the functional terms should not be read in open contradiction with the whole content of the description.…."*

17) DISCUSSION AND CONCLUSION ON THE GROUNDIII – LACK OF SUFFICIENCY: The claims directed to 4'-substituted nucleoside derivatives represented by general Markush formula (II) and its pharmaceutically acceptable salt and its prodrugs. The specification discloses the general method of preparation of compounds - Scheme-1 to 6 (pages 30-33). Further, the exemplified examples 1 to 23 have been described at pages 34 to 103. Also, the biological activity of the claimed compounds have been given in the patent specification and is supported by assays namely HIV-1 RT Polymerase Assay (Table-2, pages 103-105); Viking Assay/CTG to assess the antiviral potency in a multiple round HIV-1 infection assay and cytotoxicity in CellTiter-Glo Luminescent Cell viability assay (CTG) (Table-3, pages 105-108); Antiviral persistence assay to assess the persistence of antiviral activity upon removal of the nucleoside using MT4-GFP cell (Table-4, pages 108-112); and Adenosine Deaminase (ADA) Half-life (Table-5, pages 112-115).The assertion made by the opponent are not considered valid and the ground is dismissed.

18)Section 14 Hearing and discussion:

The objections were raised under the heading of definitiveness ,invention u/s 2(1)(ja) in view of D1-D4,u/s 3(d),3(e)and other formal requirements. The applicant clearly illustrates the structural and functional differences with respect to cited prior art D1-D4 .

D1: EP2177527(D1 OF Pre-grant)

D2: WO2013138236

D3 - KAZUHIRO HARAGUCHI ETAL, "Synthesis of 4'-Ethynyl-2'-deoxy-4'-thioribonucleosides and Discovery of a Highly Potent and Less Toxic NRTI", ACS MEDICINAL CHEMISTRYLETTERS, (20110908), vol. 2, no. 9.The synthesis of 4′-ethynyl-2′-deoxy-4′-thioribonucleosides was carried out utilizing an electrophilic glycosidation in which 4-ethynyl-4- thiofuranoidglycal 16 served as a glycosyl donor. Electrophilic glycosidation between 16 and the silylated nucleobases (N4- acetylcytosine, N6-benzoyladenine, and N2-acetyl-O6-diphenylcarbamoylguanine) was carried out in the presence of Niodosuccinimide (NIS), leading to the exclusive formation of the desired β-anomers 29, 33, and 36.

D4 KODAMA E-I ETAL, "4'-ETHYNYL NUCLEOSIDE ANALOGS: POTENT INHIBITORS OF MULTIDRUGRESISTANT HUMAN IMMUNODEFICIENCYVIRUS VARIANTS IN VITRO", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETYFOR MICROBIOLOGY, (20010501), vol. 45, no. 5.,(D2 OF PRE GRANT)considering the abstract defines series of 4′-ethynyl (4′-E) nucleoside analogs were designed, synthesized, and identified as being active against a wide spectrum of human immunodeficiency viruses (HIV), including a variety of laboratory strains of HIV-1, HIV-2, and primary clinical HIV-1 isolates. The submission u/s14recites with respect to D3-D4

.with respect to D2 ,the claims have been amended The compounds of D2 are disclosed as being useful treating Orthomyxoviridae virus infections, and particularly for the treatment of Human Influenza virus infections, not HIV. D3 differ from the nucleobases in the instant claims. D3 describes the synthesis of thioribonucleosides having cytosine, adenine and guanine nucleobases (compounds 32, 41, 43). It notes that "4'-substituted thymidines . . . exhibit potent anti-HIV activity" (1st par., p. 1). The objective of the paper was to compare the SI (selectivity indices) values of the thioribonucleosides to their oxygen-ribonucleoside analogs (compounds 44, 45, 46), and the conclusion put forth was that thio compounds 32, 41, 43 were less cytotoxic to MT-4 cells as compared to the oxygen analogs 44, 45, 46; and that thioguanosine 43 had an SI value 20X better than its analog 46. At most D3 has a limited teaching that S in place of O in the ribose may have less cytotoxicity MT-4 cells. It does not suggest or teach toward the compounds of the instance claims which have distinctly different bases than those in D3.The applicant has however given detailed submission with respect to prior art D1,D4in pre grant submission also There is no motivation in D3 (Haraguchi et al) for a person skilled in the art to modify the 'Adenosine' base to '7-deaza-adenosine' base .There is no coherent thread that combine the alleged prior art, i.e., teaching of one lead to second and so on. D4 (Kodama et al) teaches away from the modified nucleobase of the claimed invention. The different bases in D4 are thymine, 5-iodo-uracil, 5-ethyl-uracil, 5-bromovinyl-uracil, cytosine, 6-methyladenine, adenine, purine, 2,6-diaminopurine, hypoxantine, guanine, 6-chloroguanine. The presence of a 4'-ethynyl substituent alone does not dictate activity; instead, the effectiveness depends on the nucleobases and the overall structure of the molecule. The subject matter of claims are therefore considered inventive over the cited prior art.With respect to section 3the submission filed is satisfactory.The objections is already discussed under the grounds of pre grant and is not repeated for sake of brevity.Theclaim29 (now claim25) is dependent on the amended claims and the objection is therefore waived off.The formal objections have been met and there are no further objections.

19)Conclusion:

After thorough and careful consideration of the pre-grant oppositions filed by the Opponentunder section 25(1) of the Act, statements and evidences produced by the parties before and at the time of hearing, arguments presented by the parties during hearing, written submissions by the parties filed after hearing and in view of the above analysis and findings, I found that the grounds under Section 25(1)(e), Section 25(1)(f) and Section 25(1)(g) raised in the pre-grant oppositions are not found valid.

Having considered all the facts and submissions made by the Agent of the Applicant during hearing under section 14 of the Act and the written note of arguments filed by the Applicant after the said hearing as well as in view of all the documents on record and also on the basis of the facts and findings as mentioned in the preceding paragraphs, I am of the opinion that the objection regarding lack of inventive step under section 2(1)(ja), claims falling under section 3(d) and 3(e) of the Patents Act as raised in the hearing notice u/s 14 are waived off.

Hence, in this instant patent application number 201617031899, I hereby proceed with grant of patent in accordance with Section 15 of The Patents Act, 1970 (as amended). The pre-

grant opposition as filed under section 25(1) of The Patents Act, 1970 (as amended) and corresponding rule 55 of The Patents Rules, 2003 (as amended) is disposed herewith.

Dated 31 March 2025 **-Sd/-**

SWETA RAJKUMAR
Deputy Controller of Patents & Designs