PATENT COOPERATION TREATY

PCT

THIRD PARTY OBSERVATION

(PCT Administrative Instructions Part 8)

Applicant's or agent's file reference 25639	
International application number PCT/US2024/013021	International filing date (day/month/year) 26 Jan 2024 (26/01/2024)
Applicant MERCK SHARP & DOHME LLC	

Third party observation submitted by Anonymous	Observation submitted on behalf of
Date of submission(day/month/year) 30 May 2025 (30/05/2025)	Language of observation English

Basis and contents of observation

1. The observation is made on the basis of the claims in the international application as filed.
2. The observation comprises:
   References to documents: 3
   Uploaded copies of documents: 0
3. Further explanations:
   Uploaded copies of documents: 1

Citation # 1 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2015/143712	A1

Patent Applicant/Patent Owner:	Title of invention:
Merck Sharp and Dohme Corp., et al	4'-Substituted Nucleoside Reverse Transcriptase Inhibitors

Link to document:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015143712

Publication Date:	Filing Date:	Priority Date:
01 Oct 2015 (01/10/2015)	28 Mar 2014 (28/03/2014)	27 Mar 2014 (27/03/2014)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Abstract; pp. 2–3, 6–11, 15–24; Claims 1–2, 4–9, 11–14, 16–17, 19–20	1-22

Brief explanation of relevance:

Brief Explanation of Relevance:-

WO2015143712 (WO712), an earlier application by Merck, Applicant of the present Application, WO2024163262 (WO262), relates to compounds of Formulae II and I (when R is pyrrolopyrimidine) as inhibitors of reverse transcriptase (RT), and compositions, and methods thereof (Abstract; p.2).
WO712 claims a nucleoside analogue (Claim 15, Compound 4; Compound 4, Table 3, p.83), which is now identified as MK-8527 (Refer Additional Comments), and envisages prodrugs thereof.
It may be noted that Table I in the Additional Comments accompanying the TPO provides a comparison of the claims of WO262 with the claims and/or disclosures of WO712.

WO712 discloses and/or claims (Claims 1–2, 4–9, 11–14; pp.2–3, 6–11, 15–17):
1. Compound of formula I, a tetrahydrofuran (THF)/modified sugar moiety, wherein R, at position 1', is pyrrolopyrimidine, or a compound of formula II (pyrrolopyrimidine attached to THF), with the following substitutions:
1.a) X is O; Y is C≡C-R8 (ethynyl) (when R8 is H); R3 is H;
1.b) R1 (at 5'-position) is H, -C(O)R6, -C(O)OR6, a mono/di/tri-phosphate moiety or a prodrug modification thereof (e.g., McGuigan type prodrugs, pp.15–16) [i.e., ester, carbonate ester, phosphoramidate prodrugs explored at 5'-position on THF]

1.c) R2 (at 3'-position) is H, -C(O)R6a, or -C(O)OR6a [i.e., ester, carbonate ester prodrugs explored at 3'-position on THF]
1.d) On the pyrrolopyrimidine ring, R9 is H; R5 is halo (e.g., Cl; pp.7–8, 10)
1.e) R4 on the pyrrolopyrimidine ring is -N(Rx)2 [wherein Rx is H], -NHC(O)OR6b, -N(C(O)OR6b)2, NHC(O)R6b [i.e., amino, amide or carbamate moieties explored at 4-position on nucleobase]
1.f) R6, R6a, R6b can be –(C1–6 alkyl), or –(C1–3 alkylene)m, which is further attached to C3–7 cycloalkyl (e.g., cyclohexyl, pp.9–10) aryl (e.g., phenyl, naphthyl, p.10), 4–7 membered heterocycloalkyl, 5–6-membered monocyclic heteroaryl (e.g., pyridyl, p.10), or 9–10-membered bicyclic heteroaryl; the said alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group optionally substituted with R7; R7 is C1–6 alkyl, aryl or 5–6-membered heteroaryl; m is 0 or 1
2. The compound may be used as a prodrug (p.19). Prodrugs of compound of formula I can exhibit enhanced lipophilicity compared to the parent compound. A prodrug moiety can be formed by replacing the H of the alcohol/ carboxylic acid/amine group with groups such as (alkoxycarbonyloxy) alkyl, (alkanoyloxy) alkyl, etc (pp.15–17)
3. Pharmaceutical composition comprising the claimed compound, or its prodrug or salt and a pharmaceutically acceptable carrier; and further comprising an anti-HIV agent (Claims 16, 19–20; pp.9, 17–21)
4. Compound can be administered (injected) parenterally. Injectable solutions can be prepared using known methods (p.21)
5. Method for inhibiting HIV RT, by administering the claimed compound, or its prodrug, or a composition thereof (pp.17–20)
6. Method for treatment/prophylaxis of HIV or for treatment/prophylaxis/delay in onset or progression of AIDS, by administering the claimed compound/composition; the method further comprising administering claimed compound in combination with other HIV antiviral agent which is directly or indirectly effective in inhibiting HIV, treatment/prophylaxis of HIV infection and/or treatment/prophylaxis/delay of AIDS (Claim 17; pp.17–20, 22–24)
7. Daily dose of the compound can be modified depending on compound's potency o or the individual response; the compound can be formulated for extended or controlled release, and can be administered as a single dose, once-daily or less frequently (p.22)
8. The claimed compound for use in preparation of a medicament for inhibiting HIV RT, for treatment/prophylaxis of HIV infection, etc. (pp.17, 19)

The present Application, WO262, claims nucleoside RT inhibitors of Formulae I–VI, comprising the 4-amino-2-chloro-pyrrolopyrimidine nucleobase attached to THF substituted with 2-ethynyl, 2-CH2-OH and 3-OH groups, and several prodrugs thereof (including ester, carbonate esters, phosphoramidate, amide, carbamate, etc) explored at position 4 of nucleobase and 3'- or 5'-position on THF (Claims 1–9); certain specific compounds (Claims 10–11); compositions and methods thereof (Claims 12–20); claimed compound and composition for use (Claims 21–22). It may be noted that WO262 relates to prodrugs of Compound A (p.2 of WO262), which is now identified as MK-8527.

However, WO712 already claims and/or discloses the identical categories of prodrugs including ester, carbonate ester, phosphoramidate, amide, carbamate, etc comprising the alkyl, hetero/aryl, hetero/cycloalkyl groups as terminal groups, for identical nucleoside analogue of pyrrolopyrimidine attached to 2-ethynyl-THF (including MK-8527), compositions thereof and methods therewith.

Hence, all claims of WO262 lack novelty, to the extent of overlap, and lack inventive step.

Citation # 2 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2020/044257	A1

Patent Applicant/Patent Owner:	Title of invention:
Glaxosmithkline Intellectual Property (No. 2) Limited; VIIV Healthcare Company	Compounds useful in HIV therapy

Link to document: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2020044257		
Publication Date: 05 Mar 2020 (05/03/2020)	Filing Date: 28 Aug 2019 (28/08/2019)	Priority Date: 30 Aug 2018 (30/08/2018)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
pp.3–4, 9–23, 27-31; Claims 1–12, 14–21	1-22

Brief explanation of relevance:

WO 2020/044257 (WO'257) relates to compounds of Formulae I, Ia, II and IIa, their salts, pharmaceutical compositions thereof and methods for treatment and prevention of HIV. Specifically, it claims prodrugs of the nucleoside reverse transcriptase translocation inhibitor (NRTTI), 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EfdA, p.27; also known as *islatravir*), that are capable of modulating the physicochemical properties, facilitating multiple dosing paradigms and improving pharmacokinetic or pharmacodynamic profiles (substantially reducing aqueous solubilities, and facilitating a slow release, parenteral dosing modality) and enhancement in antiviral persistence (pp.27–28).

WO'257 claims NRTTI compounds with prodrug forming moieties at three positions of the 2'-deoxyadenosine scaffold that is, at the 4-amino position of the adenosine ring; and at the 2-hydroxymethyl and 3-hydroxy position of the tetrahydrofuran (THF) ring, to give carbonate, carbamate and amide type prodrugs (pp.9–11). The compounds claimed (Claim 10) and exemplified in WO'257 (Table 1; pp.13–15) have been compared to the Compounds of the present Application, WO2024163262 (WO'262; Claims 1–11; Examples 1–227; pp.56–155 of WO'262) in Table 2 of the accompanying Additional Comments hereto.

WO'257 claims and/or discloses Compounds of Formulae I, Ia, II, IIa, wherein (pp. 3–4, 9–13):
i. NR1R2 (substituent on 4-amino position of adenosine ring), wherein R1 and R2 can each be H or -C(=O)-O-(C1-6) alkyl (forming carbamate prodrug), or -C(=O)-(C1-25) alkyl (forming amide prodrug) (pp.9-12; Claims 1-3)
ii. R3 (substituent at 3-OH position on THF) is H or -C(=O)-O-R4, where R4 is (C1-6) alkyl or (C1-25) alkyl (forming ester or carbonate ester prodrug) (pp.10–11; Claims 1, 5-6)
iii. R5 (substituent at 5-hydroxymethyl position on THF) is selected from a group consisting of H, with ester, or carbonate ester prodrug moieties attached to R6, R7 or R8; wherein R6, R7 and R8 can be (C1–20) alkyl (pp. 9-11; Claims 1, 7–8
iv. X can be Cl (pp. 9-11; Claims 1)

Thus, the prodrug moieties disclosed in Formulae I, Ia, II, IIa, and exemplified contain the carbamate, carbonate, amide prodrugs, comprising a range of the alkyl chain length, including both the short and long chain alkyl groups.
Further, WO'257 also discloses and/or claims:
a) pharmaceutical composition comprising the compound and an excipient, in a parenteral form (long-acting formulation) (Claims 11–12; pp.15, 17, 23, 28–31)
b) Method of treating or preventing HIV infection, comprising administering the compound or pharmaceutical composition, further comprising administering one or more anti-HIV agents (Claims 14–17; pp.15–16, 22–23)
c) Compound for use in treating or preventing HIV infection; and its use in manufacture of medicament for use in treating or preventing HIV (Claims 18–21; pp.16)
d) Compound employed alone or in combination with other therapeutic agents (anti-HIV agents) (pp.17–22)

The present application WO'262 claims prodrugs of 4'-substituted NRTI, specifically prodrugs of an NRTTI compound (Compound A) (which is now identified as MK-8527) and their use in HIV. WO' 262 claims nucleoside reverse transcriptase inhibitor compounds of Formulae I–VI, relating to prodrugs of MK-8527 (including ester, carbonate esters, phosphate esters, phosphoramidate, amide, carbamate, etc) explored at 4^{th} position of nucleobase and 2nd or 3rd position on THF (Claims 1–9); specific compounds (Claims 10–11); pharmaceutical compositions thereof and

methods therewith (Claims 12–20); claimed compound and composition for use (Claims 21–22).

However, WO'257 already discloses the prodrugs of NRTTI molecule, that is of EFdA (adenosine analogue). It is obvious to a person skilled in the art to apply the same prodrug strategy and moieties to any NRTTI comprising a known deaza adenosine analogue. Further, WO2015143712 (Citation 1) claims identical prodrugs, including ester, carbonate ester, amide, phosphoramidate, etc., explored for nucleoside analogue identical to that claimed in WO262 (MK-8527; Claim 15-Compound 4). The present Application merely applies the same prodrug strategies disclosed in WO'257 and WO'712 to a known nucleoside molecule (MK-8527) having NRTTI activity, for the treatment and prevention of HIV.

Thus, all the claims of WO'262 lack inventive step.

Citation # 3 (Patent/utility model) (# uploaded documents: 0):

Country code:	Publication number:	Document kind code:
WO	2021/021717	A1

Patent Applicant/Patent Owner:	Title of invention:
Brii Biosciences, Inc.	Adenosine derivative and pharmaceutical composition comprising the same

Link to document:
https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2021021717

Publication Date:	Filing Date:	Priority Date:
04 Feb 2021 (04/02/2021)	27 Jul 2020 (27/07/2020)	27 Sep 2019 (27/09/2019)

Source of Abstract:	Accession number:	Publication Date of Abstract:	Retrieval Date of Abstract:

Most relevant passages or drawings:	Relevant to Claims:
Abstract, pp.1–4, 6–7, 10–11, 18–24, 30, 40–52; Claims 1, 24, 34, 36–44, 47–49	1-22

Brief explanation of relevance:

WO2021021717 (WO717) discloses adenosine derivative prodrugs that have HIV reverse transcriptase inhibitory activity, as well as stereoisomer, salt, tautomer or solvate thereof, and pharmaceutical compositions thereof that can be used for the treatment of HIV infection (Abstract, pp.1, 3).

WO717 discloses that 4'-ethynyl-2-fluoro-2'-deoxyadenosine (EFdA, MK-8591, islatravir), modified EFdAs and prodrugs have been previously disclosed (p.2).

WO717 discloses and/or claims adenosine prodrug derivatives of Formula I, that can undergo conversion to a target drug (i.e., EFdA) (p. 30), wherein (pp.3–4, 18–21; Claim 1):
(a) The nucleobase is 2-halo-adenosine; the halo (X) may be fluoro or chloro (pp. 4, 11, 22, 24)
(b) A tetrahydrofuran (or modified sugar) moiety is attached to the nucleobase and is substituted with ethynyl at position 2 of tetrahydrofuran (= position 4' of the sugar moiety).
(c) Prodrug moieties are explored at the 4-amino of the adenosine (R2) and at positions 2 and / or 3 of the tetrahydrofuran (R1 and R1') (= at positions 5' and 3' of the modified sugar respectively).
(d) The prodrug moieties may be -C(O)OR4, i.e. carbonates, where R4 may be H, C1-10 alkyl, C3–10 optionally substituted cycloalkyl (fused or bridged ring systems having up to 20 C atoms, such as adamantyl), 3-to 10-membered heterocycloalkyl (fused or bridged ring systems), aryl, or heteroaryl (such as pyridyl) (pp.3, 10–11). Thus, it may be noted that WO717 discloses ester prodrugs including those with adamantyl, aryl and heteroaryl groups at the terminal end.
(e) The prodrug moiety may be an ODOL moiety, i.e., 5-methyl-2-oxo-1,3-dioxol, when R1, R2 or R3 is R5 (where R9 is H or C1–10 alkyl; R6 is H or C1–10 alkyl), whether with or without a linker [R5 or –L1-R5 or Z-L4-R5; where -Z- is a divalent -C(O)- or -C(O)O-; and L4-R5 is –(C1–10 alkylene)-O-R5; formula 9: pp. 27–29] (p.6; also pp. 23–24, Claim 24: formulae 4, 6, 4B; Claim 34).

WO717 also discloses and/or claims:

(f) Pharmaceutical composition comprising one or more claimed adenosine derivatives, salts, stereoisomers or combinations thereof, and one or more pharmaceutically acceptable carriers, suitable for administration via various modes, including parenteral; it may be a long-acting injectable composition (pp.7, 30, 40–42; Claims 36–44).
(g) Such composition further comprising one or more anti-HIV agents (pp.41–42)
(h) Method for treating or preventing HIV infection therewith, including where the HIV infection is caused by wild-type HIV or drug resistant HIV, and wherein the administration schedule is a daily, weekly, biweekly or monthly administration (pp.7, 42–52; Claims 47–49)
(i) Use of the claimed pharmaceutical composition for treating AIDS, wild-type HIV, drug resistant HIV (p. 50).

Further, Brii Biosciences, Inc. has filed the following related applications:
A) WO2022159872 (WO872; Citation 3A) which claims similar adenosine derivative prodrugs with a terminal adamantyl or other macrocyclic prodrug moiety; pharmaceutical composition thereof, either alone or in combination thereof with other anti-HIV agents, including lenacapavir, cabotegravir, etc.; method of treating or preventing HIV therewith [Claims 1, 16, 28, 30–58 of WO872].
B) WO2022159877 (WO877; Citation 3B) which claims combination of a capsid inhibitor (lenacapavir) and adenosine derivative (EFdA) prodrugs that are also disclosed in WO717 and method of treating HIV therewith, where the adenosine derivative is administered (i) orally once every week to once every 8 weeks, (ii) via subcutaneous and/or intramuscular injection once every month or up to once every 12 months [Abstract; p.60, Claims 1–79 of WO877]

The present Application, WO2024163262 (WO262) claims prodrugs of similar 4'-substituted nucleoside reverse transcriptase inhibitors, where prodrug moieties are attached at the 4-amino position of the pyrrolopyrimidine core and / or 3'- and 5'- positions of the tetrahydrofuran (R2 and R3) (p.6, Claims 1–11), pharmaceutical composition thereof, either alone or in combination with other anti-HIV agents (Claims 12–14), method for inhibition of HIV reverse transcriptase and treating HIV, etc (Claims 15–20) and use thereof (Claims 21–22) . It may be noted that compounds claimed in WO262 include carbonate ester prodrugs with a terminal ODOL, adamantyl, aryl, cycloalkyl, heteroaryl or alkyl moiety (Claim 11). The nucleobase of WO262 can be considered to be a deaza analogue of EFdA.

A comparison of the prodrugs claimed in WO717 and the present Application, WO462, is set out as Table III in the Additional Comments.

In light of WO717 (disclosing carbonate ester prodrugs of EFdA), read alone or with WO872 and WO877 (Citations 3A and 3B respectively), Claims 1 to 22 of WO262, lack inventive step to the extent that they relate to carbonate ester prodrugs of adenosine derivative.

ADDITIONAL COMMENTS FOR WO 2024/163262

The following comments are being offered in respect of International Application Number PCT/US2024/013021 published as WO 2024/163262 (WO'262) filed by Merck Sharp and Dohm LLC and titled "Prodrugs of 4'-substituted nucleoside reverse transcriptase inhibitors".

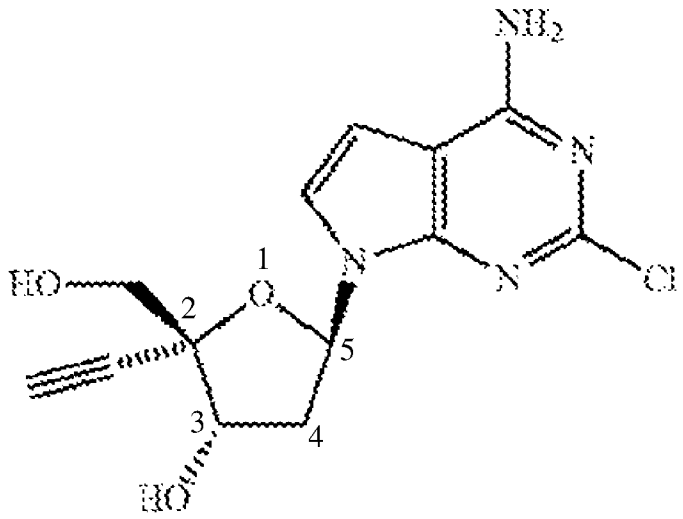
The Additional Comments are being filed along with the accompanying Third-Party Observation to point out the (A) Interchangeable nomenclature for chemical compounds, (B) lack of novelty to the extent of overlap and lack of inventive step of the claims of the present Application, WO'262 and (C) Validity of priority date.

A. NOMENCLATURE OF THE COMPOUNDS

It may be noted that the naming and numbering of chemical compounds can be done in more than one way. The compounds of the present Application are termed as 4'-substituted nucleosides, wherein the nucleobase (pyrrolopyrimidine ring) is attached to the 1'-position of a modified sugar moiety; in the modified sugar moiety, the ribose sugar is replaced with a 2'-deoxy-3'-hydroxy-4'-ethynyl-4'-(hydroxymethyl)- furanose ring.

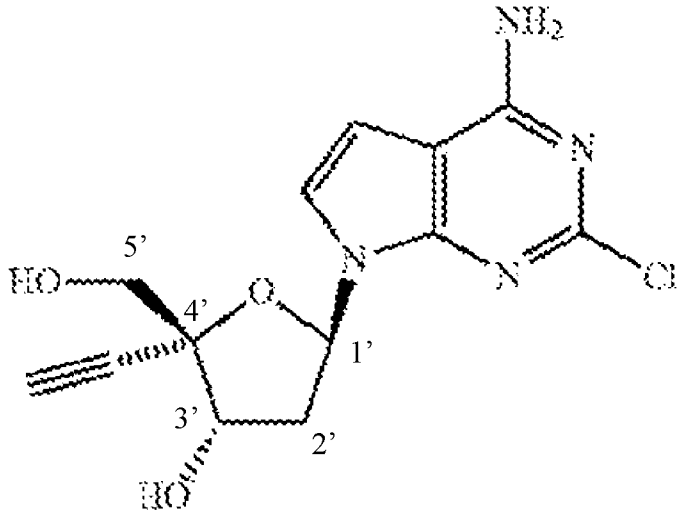
The 5-membered modified ribose ring has been referred to using different numbering in the present Application, WO'262. For example, WO'262 describes that the prodrugs of Compound A are substituted at the 3' (or 3) position, the 5' (or 5) position, or both of the tetrahydrofuran (THF) ring, which may also be referred to as the sugar moiety (p.6 of WO'262).

Numbering followed when, the 5-membered ring is considered as Tetrahydrofuran is as follows:



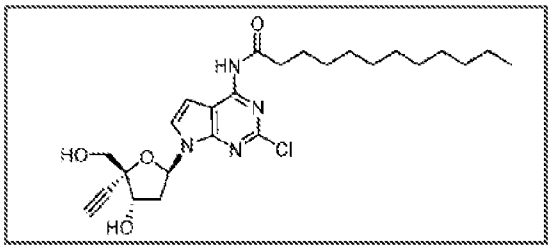
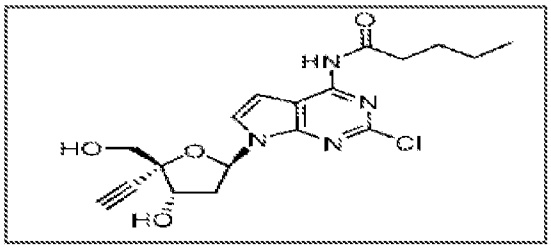
(A).

Numbering followed when, the 5-membered ring is considered as modified ribose moiety, is as follows:

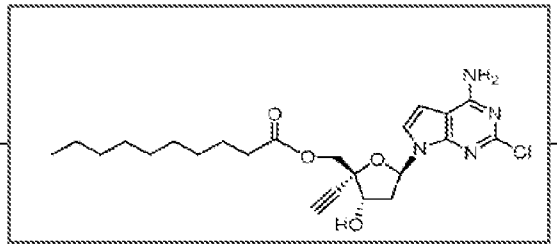
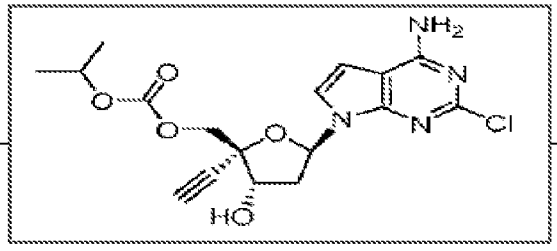


(A).

The IUPAC nomenclature of the compounds differs depending on the position at which the prodrug forming substitutions are made. For example, the IUPAC nomenclature of Examples 21 and 22 (pp.70–72), when the prodrug moiety is attached to the 4-amino of the nucleobase, refers to the compounds with substitutions on the THF ring as -5-ethynyl-4-hydroxy-5(hydroxymethyl)tetrahydrofuran. This can also be termed as 2-ethynyl-2-hydroxymethyl-3-hydroxy-tetrahydrofuran.

	
Example 21: N-(2-chloro-7-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4yl)dodecanamide	Example 22: N-(2-chloro-7-((2R,4S,5R)-5-ethynyl-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)pentanamide

On the other hand, the IUPAC nomenclature of Examples 20 (pp.68–69) and 23 (p.72), when the prodrug moiety is attached to the modified sugar moiety or the THF ring, refers to the tetrahydrofuran ring as 2-substituted-2-ethynyl-3-hydroxytetrahydrofuran.

Example 20: ((2R,3S,5R)-5-(4-amino-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl decanoate	Example 23: ((2R,3S,5R)-5-(4-amino-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl(-2-ethynyl-3-hydroxytetrahydrofuran-2-yl)methyl isopropyl carbonate

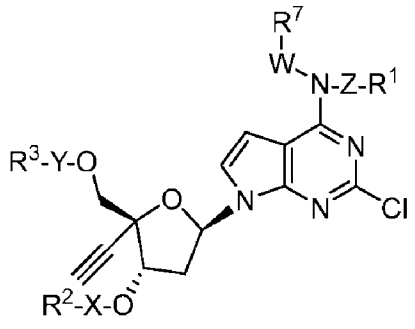
B. Lack of Novelty to the Extent of Overlap and Lack of Inventive Step

As shown below and pointed out in the accompanying Third Party Observation (TPO), all claims of the present Application, WO'262, lack novelty to the extent of overlap and lack inventive step.

B.1. Claims of the Present Application, WO'262

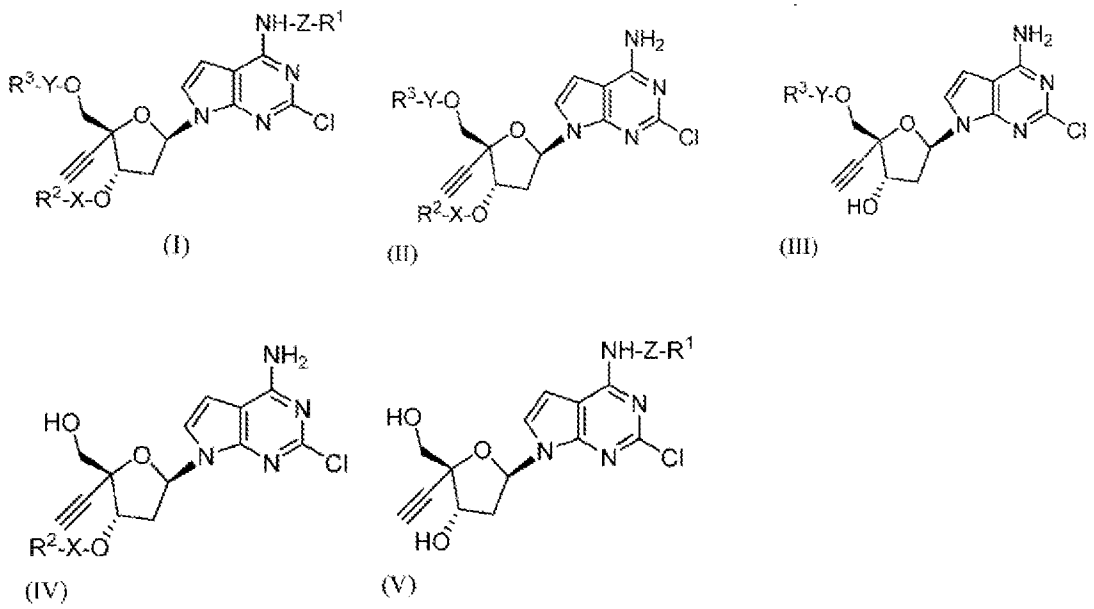
The present Application, WO'262, claims (Claims 1–9):

1) Compounds of Formula VI



(VI)

Or derivative Markush structures thereof, Formulae I to V



comprising the 2-chloro-4-amino-pyrrolopyrimidine nucleobase attached to the 2-ethynyl-tetrahydrofuran ring. [It may be noted that the parent molecule, Compound A (p.2 of WO'262) is MK-8527, which is being investigated as a nucleoside reverse transcriptase translocation inhibitor; https://lapal.medicinespatentpool.org/compounds/mk-8527#information; last accessed on 30.05.2025].

2) Compounds of Formulae I to VI, wherein,

Z and W are -C(=O)-, -C(=O)-O-, and a bond. Thus, the prodrug moieties explored at the 4-amino position on the pyrrolopyrimidine ring are amide or carbamate prodrugs.

Y is -C(=O)-, -C(=O)-O-, -CR^5R^6-O-C(=O)-, -CR^5R^6-O-C(=O)-O-, P(=O)(O-C6-12 aryl)-NH-CR^4C(=O)-O- and a bond. Thus, the prodrug moieties explored at the 2-hydroxymethyl position on the THF ring are ester, carbonate ester, alkoxy alkyl ester, alkoxyalkyl carbonate ester, phosphoramidate (ProTide)], etc.

X is selected from -C(=O)-, -C(=O)-O-, -CR^5R^6-O-C(=O)-, -CR^5R^6-O-C(=O)-O-, and a bond. Thus, the prodrug moieties explored at the 3-hydroxy position on the

THF ring are ester, carbonate ester, alkoxy alkyl ester, alkoxy alkyl carbonate ester, etc.

It may be noted that, the present Application, WO'262, claims 227 compounds in Claim 10, and a subset of these (14 compounds) in Claim 11.

The accompanying TPO points out that all the categories of prodrugs explored for the three positions of the nucleoside analogue have already been claimed and/or disclosed in the prior art documents, including for MK-8527. Thus, the claims of the present Application, WO'262 lack novelty and/or inventive step.

3) WO'262 also claims the pharmaceutical composition (injectable) comprising the claimed compound, and one or more additional therapeutic agents (Claims 12–14). WO'262 further claims method therewith, for inhibiting HIV reverse transcriptase, method of treating or preventing HIV, method of treatment, prophylaxis or delay in onset or progression of AIDS, and the compound or composition for use in the manufacture of medicament for inhibiting HIV reverse transcriptase, for treating or preventing HIV, or for treatment, prophylaxis or delay in onset or progression of AIDS, or for use in therapy (Claims 15–22). These claims too lack inventive step in light of the prior art documents referred to in the TPO.

B.2. Comparison of disclosures of prior art with claims of the Present Application, WO'262

The following tables show how the prior art documents disclose similar or identical nucleosides, and prodrugs thereof, which are structurally similar to those claimed in the present Application, WO'262.

Tables I to _ below show the comparison of the disclosures and claims of the prior art documents cited in the accompanying TPO—WO2015143712 [Citation 1], WO2020044257 [Citation 2], and WO2021021717 [Citation 3] respectively—with the claims of the present Application, WO'262.

TABLE I: COMPARISON OF PRIOR ART WO 2015/143712 (WO'712) AND THE PRESENT APPLICATION WO 2024/163262 (WO'262)

WO2015143712 (WO'712), an earlier application by Merck Sharp and Dohme Corp., the Applicant of the present Application, WO'262, claims and/or discloses similar 4'-substituted nucleoside reverse transcriptase inhibitors as those claimed in WO'262, and similar prodrug moieties explored at the three positions – 4th position of the pyrrolopyrimidine ring, and the 3' and 5' position of tetrahydrofuran (THF) moiety. WO'712 also claims a nucleoside analogue (Claim 15, Compound 4; Compound 4, Table 3, p.83), which is now identified as MK-8527 (https://lapal.medicinespatentpool.org/compounds/mk-8527#information; last accessed on 30.05.2025), and envisages prodrugs thereof.

The Table I below provides a comparison of the structural aspects and substituents claimed in Markush Formulae I–VI in WO2024163262, and those disclosed and/or claimed in the Markush Formulae I and II of the prior art document WO'712. The table shows the extent of the overlap between the structural components as well as the other aspects of pharmaceutical composition, methods and use, previously disclosed and claimed in WO2015143712 with that of the present Application, WO'262, for nucleoside reverse transcriptase inhibitors, and the several prodrugs thereof.

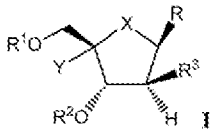
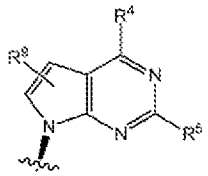
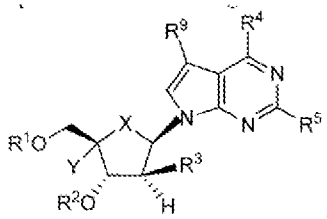
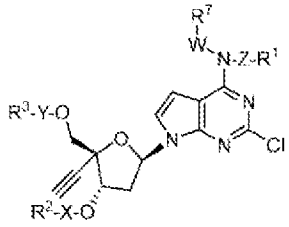
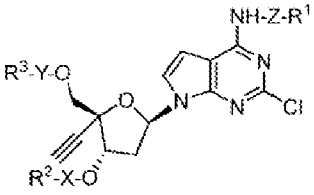
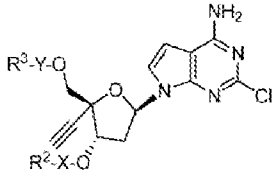
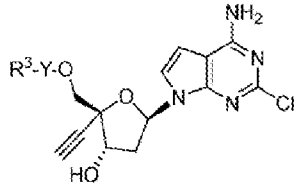
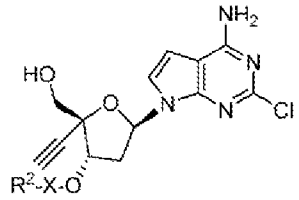
Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
1. Markush Formulae Compound of Formula I  I, wherein, **R** is  or, compound of Formula II,  II,	**1.Markush Formulae** Compounds of Formula VI or derivative markush structures of Formulae I–V  (VI)  (I)  (II)  (III)  (IV)	WO'712, thus, discloses the derivatives or prodrugs for the nucleoside analogue of Formula II (or Formula I, when R is pyrrolopyrimidine), which is identical to the nucleoside analogue in the present Application, WO'262, when X is O, Y is ethynyl, R3 is H, R5 is Chlorine, R9 is H and R4 is amino or a derivative thereof. Further, as shown in Column 1, WO'712 also discloses the following prodrug moieties: (i) At the 4-amino position on the pyrrolopyrimidine ring: amide, carbamate (ii) At the 2-hydroxymethyl position: ester, carbonate ester or a phosphate-based ester (iii) At the 3-hydroxy position: ester, carbonate ester (iv) Possible prodrugs formed by replacing H of alcohol group or H of the carboxylic acid group with groups such as (alkoxycarbonyloxy) alkyl, (alkanoyloxy) alkyl, etc The prodrug moieties disclosed in WO'712 comprise the ester, carbonate

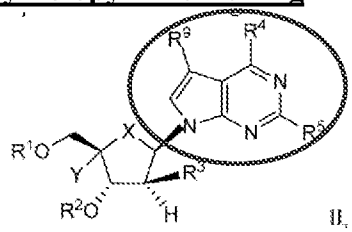
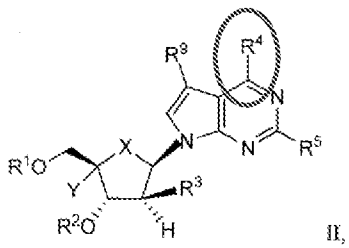
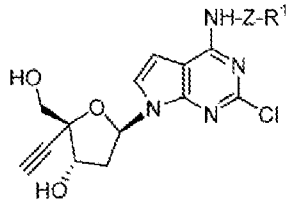
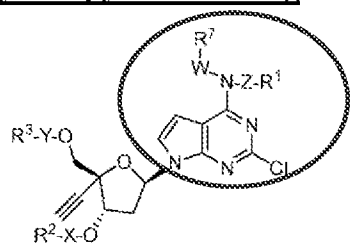
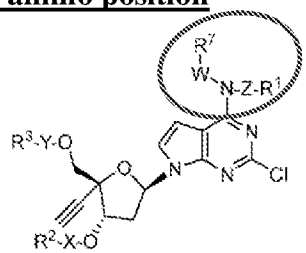
Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
wherein, **2. Nucleobase - pyrrolopyrimidine ring**  II, i. R9 is H ii. R5 is halo (e.g., Cl; pp.7–8, 10) **4-amino position**  II, i. R4 is -N(Rx)2 [when Rx is H, it gives 4-amino group], -NHC(O)OR6b, -N(C(O)OR6b)2, NHC(O)R6b [i.e., amino group or the amide or carbamate prodrug moieties at the 4-position of the pyrrolopyrimidine ring]; wherein R6b can be	 (V) wherein, **2. Nucleobase - pyrrolopyrimidine ring**  (VI) i. Chloro substitution at the 2nd position ii. Amino or derivative thereof at the 4th position **4-amino position**  (VI) i.Z and W is -C(=O)-, -C(=O)-O-, and a bond [the prodrug moiety at the 4-amino position could be the amide or carbamate moiety] ii.R1 is H, C1–21 alkyl, $(CR^5R^6)_z$-C3–12cycloalkyl, (CR^5R^6)z-C5–12 heterocyclyl, (CR^5R^6)z-C6–12 aryl,	ester, amide, carbamate, etc functional groups attached to alkyl chains, which may further be attached to optionally substituted cycloalkyl, heterocycloalkyl, aryl or heteroaryl groups. Thus, in light of WO'712 Claims 1–9 of the present Application, WO'262 lack novelty to the extent of overlap and lack inventive step. Further, Claims 10 and 11, which claim the specific compounds of Claims 1–9 also lack inventive step in light of WO'712.

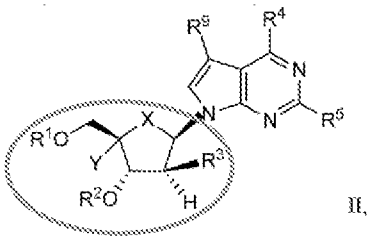
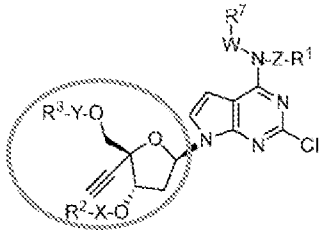
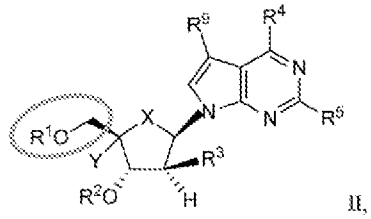
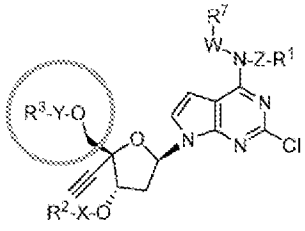
Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
–(C1–3 alkylene)m, which is further attached to C3–7 cycloalkyl, aryl, 4–7 membered heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, **or** 9 or 10-membered bicyclic heteroaryl; wherein the said cycloalkyl, aryl, heterocycloalkyl or heteroaryl group can be optionally substituted with R7; R7 can be C1–6 alkyl, aryl or 5–6-membered heteroaryl; m is 0 or 1	$(CR^5R^6)z$-C5–12 heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with 1–3 groups from halo, C1-6 alkyl, C3-12 cycloalkyl and hydroxy; z is 0–6 iii. R7 is H, C1–21 alkyl, $(CR^5R^6)_z$-C5–12cycloalkyl; z is 0–6	
3.Tetrahydrofuran ring  II, i. X is O, ii. Y is ethynyl (R8 is H) iii. R3 is H	**3. Tetrahydrofuran ring**  (VI) i. 2-ethynyl substitution ii. Derivatization explored at 2-hydroxymethyl and 3-hydroxy position	
2-hydroxymethyl position  II, i. R1 is H, -C(O)R6, -C(O)OR6, a mono/di/tri-phosphate moiety or a prodrug modification	**2-hydroxymethyl position**  (VI) i. Y is -C(=O)-, -C(=O)-O-, $-CR^5R^6$-O-C(=O)-, $-CR^5R^6$-O-C(=O)-O-,	

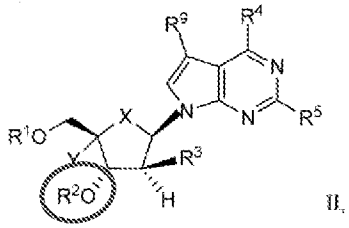
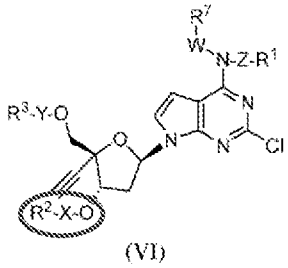
Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
thereof [i.e., the prodrug moiety at the 2-hydroxymethyl position can be an ester, carbonate ester or a phosphate-based ester, e.g., McGuigan type prodrugs (pp.15–16)]; ii. wherein, R6 can be –(C1–6 alkyl), or –(C1–3 alkylene)m, which is further attached to C3–7 cycloalkyl, aryl, 4–7 membered heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, **or** 9 or 10-membered bicyclic heteroaryl; wherein the said alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group can be optionally substituted with R7; iii. R7 can be C1–6 alkyl, aryl or 5–6-membered heteroaryl; iv. m is 0 or 1	P(=O)(O-C6-12 aryl)-NH-CR^4C(=O)-O- and a bond; [i.e., the prodrug moieties formed at the 2-hydroxymethyl position, includes esters, carbonate esters, alkoxycarbonyl ester, alkoxycarbonyloxy ester, phosphoramidate (ProTide)] ii. wherein, R5 and R6 can be H, halogen, C1–3 alkyl, C3–6 cycloalkyl; iii. R4: H, C1–3 alkyl, (CH2)z-cycloalkyl iv. R3 is H, C1–21 alkyl, $(CR^5R^6)_z$-C3–12 cycloalkyl, (CR^5R^6)z-C5–12 heterocyclyl, (CR^5R^6)z-C6–12 aryl, (CR^5R^6)z-C5–12 heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with 1–3 groups from halo, C1-6 alkyl, C3-12 cycloalkyl and hydroxy; v. z is 0–6	
3-hydroxy position  II. i. R2 is H, -C(O)R6a, or -C(O)OR6a [i.e., the	**3-hydroxy position**  (VI) i. X can be -C(=O)-, -C(=O)-O-, -CR^5R^6-O-	

Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
prodrug moiety at the 3-hydroxy position can be an ester or carbonate ester]; ii. wherein, R6a can be –(C1–6 alkyl), or –(C1–3 alkylene)m, which is further attached to C3–7 cycloalkyl, aryl, 4–7 membered heterocycloalkyl, 5 or 6-membered monocyclic heteroaryl, **or** 9 or 10-membered bicyclic heteroaryl; wherein the said alkyl, cycloalkyl, aryl, heterocycloalkyl or heteroaryl group can be optionally substituted with R7; iii. R7 can be C1–6 alkyl, aryl or 5–6-membered heteroaryl; iv. m is 0 or 1 (Claims 1–2, 4–9, 11–14; pp.2–3, 6–11, 15–17) Also, WO'712 discloses that a prodrug moiety can be formed by replacing the H of the alcohol group or H of the carboxylic acid group or H of amine group with groups such as (alkoxycarbonyloxy) alkyl, (alkanoyloxy) alkyl, etc. (p.15 of WO'712)	C(=O)-, -CR^5R^6-O-C(=O)-O-, and a bond; wherein R5 and R6 can be H, halogen, C1–3 alkyl, C3–6 cycloalkyl ii. [i.e., the prodrug moieties formed at the 3-hydroxy position, includes esters, carbonate esters, alkoxycarbonyl ester, alkoxycarbonyloxy ester, etc] iii. R2 can be H, C1–21 alkyl, $(CR^5R^6)_z$-C3–12cycloalkyl, (CR^5R^6)z-C5–12 heterocyclyl, (CR^5R^6)z-C6–12 aryl, (CR^5R^6)z-C5–12 heteroaryl; wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with 1–3 groups from halo, C1-6 alkyl, C3-12 cycloalkyl and hydroxy; z is 0–6 Also, at least one of R^1, R^2 and R^3 is not H; [Claims 1–9 of WO'262 and claims dependent thereon]	

Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
i. Pharmaceutical composition comprising the claimed compound and a pharmaceutically acceptable carrier. ii. The pharmaceutical composition further comprising an anti-HIV agent. iii. Compounds can be administered parenterally (e.g., subcutaneous injections, intravenous, intramuscular, etc). Injectable solutions can be prepared (p.21) (Claims 16, 19–20; pp.9, 17–21)	i. Pharmaceutical composition comprising the claimed compound and a pharmaceutically acceptable carrier, wherein, the composition is injectable or adapted for injection. ii. The pharmaceutical composition further comprising one or more additional therapeutic agents [Claims 12–14 of WO'262]	WO'712, thus, discloses: (i) the pharmaceutical composition comprising the claimed compound (also in the form of its prodrugs) (ii) the compound can be administered (injected) parenterally (iii)the pharmaceutical composition can further comprise an additional anti-HIV agent. Thus, in light of WO'712, Claims 12–14 of the present Application, WO'262, lack novelty to the extent of overlap and lack inventive step.
Method for inhibition of HIV reverse transcriptase, which comprises administering the claimed compound, or a prodrug thereof, or a pharmaceutical composition thereof (pp.17–20)	Method for inhibition of HIV reverse transcriptase, which comprises administering the claimed compound or the claimed pharmaceutical composition [Claim 15 of WO'262]	WO'712, thus discloses the method for inhibition of HIV reverse transcriptase, which comprises administering the claimed compound, or a prodrug thereof, or a pharmaceutical composition thereof. Thus, in light of WO'712, Claim 15 of the present Application, WO'262, lacks novelty to the extent of overlap, and lacks inventive step.
i.Method for treatment or prophylaxis of HIV or for treatment, prophylaxis or delay in onset or	i.Method for treatment of HIV infection, or treatment, prophylaxis or delay in onset or	WO'712, thus, discloses: (i) Method for treatment of HIV infection, or treatment, prophylaxis or

Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
progression of AIDS, comprising administering the claimed compound or claimed composition; ii. the method further comprising administering the claimed compound in combination with at least one other HIV antiviral iii. an anti-HIV agent is any agent which is directly or indirectly effective in inhibition of HIV, treatment or prophylaxis of HIV infection and/or treatment, prophylaxis or delay in onset or progression of AIDS). iv. The daily dose of the compound can be modified depending on the potency of the compound or the individual response; the compound can be formulated for extended or controlled release, and can be administered as a single dose, once-daily or less frequently. (Claim 17; pp.17–20, 22–24)	progression of AIDS, comprising administering the claimed compound or the claimed pharmaceutical composition; ii. the method further comprising administering one or more additional therapeutic agents, e.g., lenacapavir; and wherein the method comprises administering the compound with a dosing interval once per month to once per every 12 months [Claims 16–20 of WO'262]	delay in onset or progression of AIDS, comprising administering the claimed compound or the claimed pharmaceutical composition (ii) the method further comprising administering the claimed compound in combination with at least one other anti-HIV agent (iii) dosing regimen of the compound can be varied. Thus, in light of WO'712, Claims 16 and 17 of the present Application, WO'262, lack novelty to the extent of overlap, and lack inventive step. Claims 18–20 of WO'262 lack inventive step
The claimed compound for use in preparation of a medicament for inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of HIV infection, or for the	The claimed compound or the claimed pharmaceutical composition for (i) use in preparation of a medicament for inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of	WO'712, thus, discloses the claimed compound for use in preparation of a medicament for inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of HIV infection, or for the

Table I		
WO2015143712 (WO712; Prior Art Document)	**WO2024163262 (WO262; Present Application)**	**Comments**
treatment, prophylaxis or delay in onset or progression of AIDS, or for therapy (pp.17, 19)	HIV infection, or for the treatment, prophylaxis or delay in onset or progression of AIDS; (ii) use in therapy [Claims 21–22 of WO'262]	treatment, prophylaxis or delay in onset or progression of AIDS, or for therapy. Thus, in light of WO'712, Claims 21 and 22 of the present Application, WO'262, lacks novelty to the extent of overlap, and lacks inventive step.

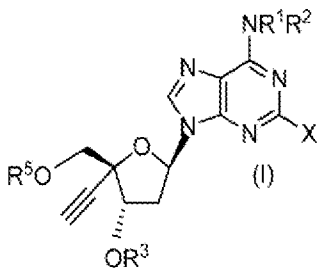
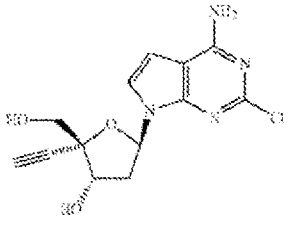
Thus, WO'712 already discloses and/or claims 4'-substituted nucleoside reverse transcriptase inhibitors and prodrugs thereof, which are identical to those claimed in the present Application, WO'262. WO'712 claims the nucleoside analogue MK-8527, and thus envisages the prodrugs of MK-8527. WO'712 also claims the pharmaceutical composition thereof, method of treatment, prophylaxis, inhibition of reverse transcriptase, etc and the said compounds for use. It may be noted that, although WO'712 does not exemplify or specifically claim the compounds claimed in Claims 10 and 11 of WO'262, these compounds of WO'262 fall within the scope of the Markush formulae I and II and the description thereof in WO'712.

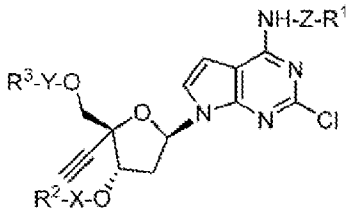
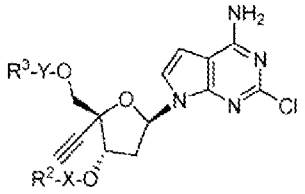
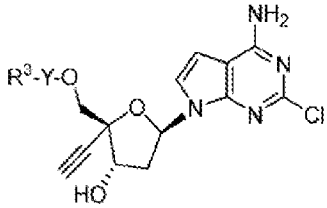
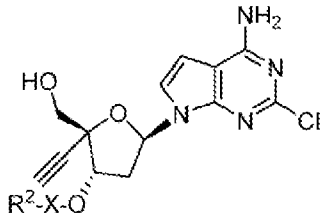
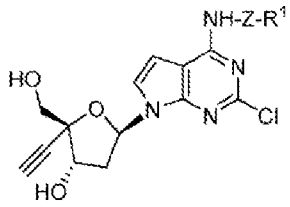
TABLE II: COMPARISON OF PRIOR ART WO 2020/044257 (WO'257) AND THE PRESENT APPLICATION WO 2024/163262 (WO'262)

The prior art patent document WO2020044257 (WO'257) discloses prodrugs for EFdA (*islatravir)*, a Nucleoside Reverse Transcriptase Translocation Inhibitor (NRTTI). WO'257 claims prodrug moieties at 3 different positions of the molecule. The type of prodrugs disclosed in WO'257 are the amide, ester, carbonate ester, and alkoxy methyl carbonate ester.

The present Application, WO2024163262 (WO'262) claims prodrugs for MK-8527, which is also an NRTTI. Some of the prodrugs claimed in the present Application, WO'262 are those with an amide, ester, carbonate ester, and / or alkoxy methyl carbonate ester, at 1, 2 or 3 different positions of the molecule.

The table below shows the comparison of the molecules and the prodrug moieties in the disclosures and claims of the prior art document, WO'257, cited as Citation 2 in the accompanying TPO, with the claims of the present Application, WO'262.

Table II		
Prior art document WO2020044257 (WO'257)	**Present Application WO2024163262 (WO'262)**	**Comments**
A. Structural difference in NRTTI molecules claimed in prior art document WO'257 and present Application WO'262		
WO'257 discloses and claims prodrugs of Formula I:  (I)	WO'262 claims prodrugs of Formula A:  (A).	It may be noted that the Formula I of WO'257 differs from Formula A of WO'262 in the modified nucleobase. While the nucleobase in Formula I of WO'257 is 2-halo-adenosine moiety,

Formula I of WO'257, wherein X is selected from F, Cl; R1, R2, R3, and R5 are H (*and further described herein below)*	Including compounds of Formulae I–VI  (I)  (II)  (III)  (IV)  (V)	the modified nucleobase in Formula A of WO'262 is 2-chloro-substituted pyrrolopyrimidine ring (i.e., deazaadenosine ring). The parent molecule for compounds enlisted in Table 1 of WO'257 (pp.13–15) is a known NRTTI (EFdA, p.27 of WO'257; also known as *islatravir).* T he parent molecule for compounds of the present Application, WO'262, is Compound A (MK-8527) which is also an NRTTI.

B. Prodrugs explored at the 4th position of the modified nucleobase in the prior art WO'257 and in the present Application WO'262

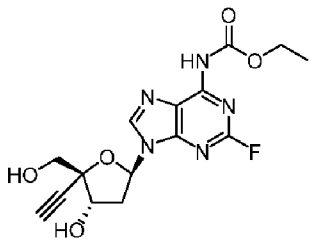
WO'257 discloses Compound of formulae I, Ia, II, IIa, wherein,

the moiety at the 4th position on the adenosine ring is -NR1R2; wherein, R1 and R2 are each independently selected from H, and C(=O)-O(C1-C6) alkyl; or C(=O)-(C1-C25) alkyl. In some embodiments R1 is H, and R2 is C(=O)-(C1-C20) alkyl, preferably C(=O)-(C1-C15) alkyl (pp.9-12). [i.e., the prodrug categories disclosed at the 4-amino position include amide, carbamate, both comprising short as well as long alkyl chain].

Some of the compounds exemplified in WO'257 have prodrugs explored at the 4th position, and are listed herein below:

Carbamate prodrugs

(i) ethyl carbamate moiety (Compound 3, p.13)

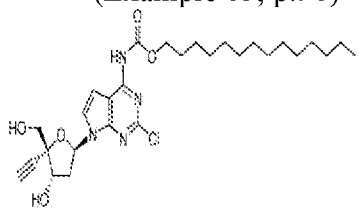


The present Application, WO'262, based on defining the variables W, Z and R1 and R7, claims that the prodrug moieties explored at the 4th position include carbamates and amides.

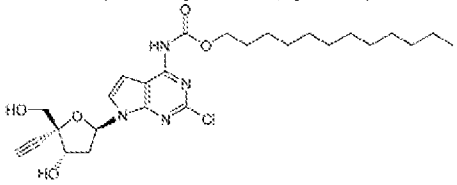
Carbamate prodrugs

Several compounds having a carbamate prodrug at the 4-amino position of the pyrrolopyrimidine ring have been claimed (Claims 10–11) and exemplified in WO'262. Some of the compounds are listed herein below:

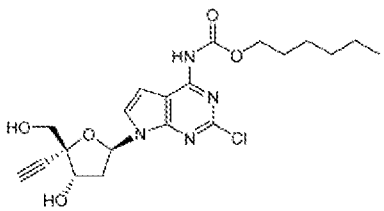
1. Tetradecyl carbamate (Example 63, p.98)



2. Dodecyl carbamate (Example 219, p.152)



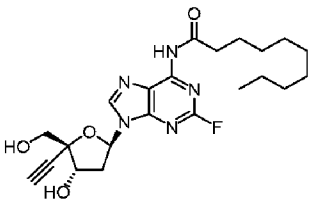
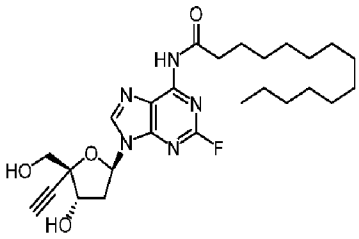
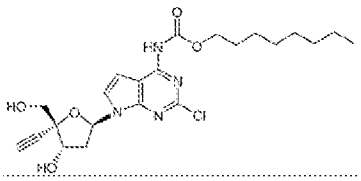
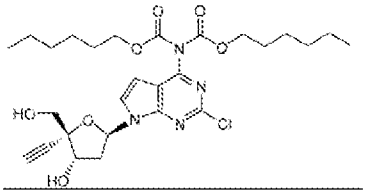
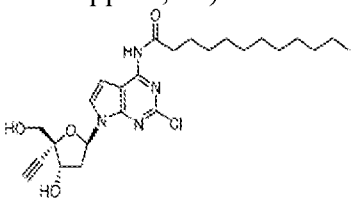
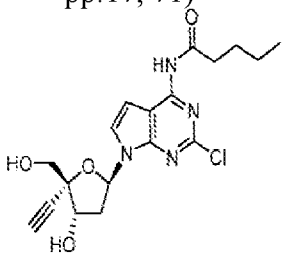
3. Hexyl Carbamate (Example 221, p.153)

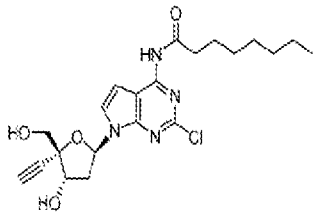
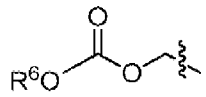
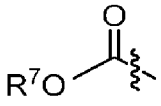
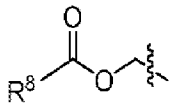
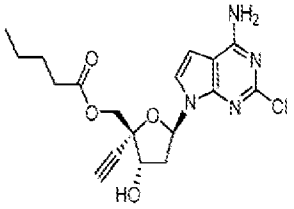


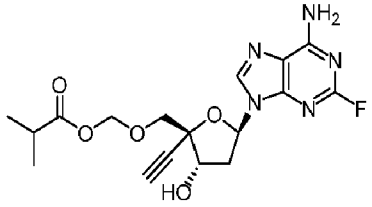
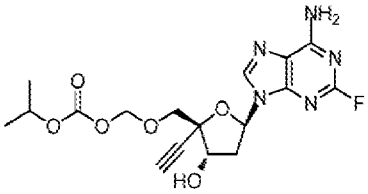
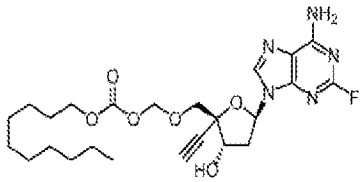
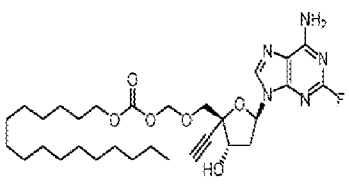
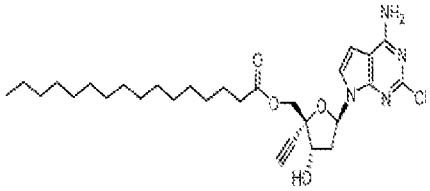
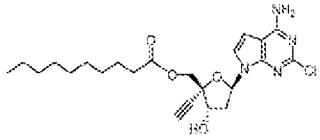
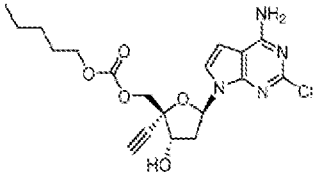
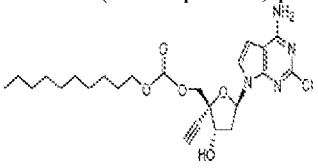
As can be seen, WO'257 discloses and claims carbamate and amide prodrugs of EFdA that may have C1-C6, or C1-C25 alkyl for the carbamate prodrug moiety; or C1-C25, or C1-C20, or C1-C15 alkyl for the amide prodrug moiety, which are explored at the 4th position of the nucleobase.

The present Application also claims C1-C21 alkyl for the carbamate or amide prodrug moieties at the same position of the modified nucleobase (pyrrolopyrimidine ring).

Thus, WO'257 already discloses such prodrug moieties at the 4th position of the nucleobase of an NRTTI compound.

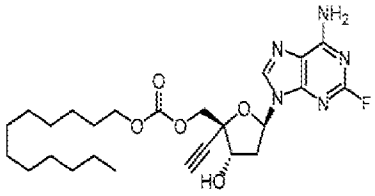
Amide prodrugs (i)Decanamide (Compound 14, p.15)  (ii) Tetradecanamide (Compound 15, p.15) 	4. Octyl Carbamate (Example 223, p. 153)  **Di-carbamate prodrugs** di-Hexyl carbamate (Example 222, p.153)  **Amide Prodrugs** 1. Dodecanamide (Example 21, pp.16, 70)  2. Pentamide (Example 22, pp.17, 71) 	Thus, with respect to these prodrug moieties substituted at the 4th position of the fused ring, the present Application, WO'262, lacks inventive step (to the extent of overlap).

	3. Octanamide (Example 66, p.102) 	
C. Prodrug substitutions at the 2-hydroxymethyl position on the tetrahydrofuran ring in the prior art document, WO'257, and the present Application, WO'262		
WO'257 discloses Compound of Formulae I, Ia, II, IIa, wherein the substituent R5 at the 2-hydroxymethyl is selected from a group consisting of H,    Wherein R6, R7, and R8 are independently selected from (C1-C20) alkyl; or R6 and R7 are selected from (C1-C25) alkyl. Various embodiments are where R6 or R7 are selected from C1-C15, or C1-C10, or C1-C6 alkyl; R8 is selected from C1-C10, or C1-C6 alkyl. [Thus, the prodrug categories disclosed at the 2-hydroxymethyl position on the tetrahydrofuran ring are ester, carbonate ester, alkoxy alkyl	The present Application, WO'262, based on defining the variables Y and R3, claims that the prodrug moieties explored at the 2nd position on the tetrahydrofuran ring includes ester, carbonate ester, alkoxy alkyl ester, alkoxy alkyl carbonate ester, etc , wherein Y is selected from C(=O), C(=O)-O, -CR^5R^6-O-C(=O)-, -CR^5R^6-O-C(=O)-O-, etc.; and R3 is selected from a group consisting of H, C1-C12 alkyl: Some of the compounds claimed (Claims 10–11) and exemplified are listed herein below: **Ester prodrugs** 1.Methyl pentanoate (Example 15, p.65).  Similarly, Examples 89 (p.114), 116 (p.122), 118 (p.122), etc disclose	As can be seen, the 2-hydroxymethyl position on the tetrahydrofuran ring has been substituted in WO'257 with various prodrug moieties, that include the ester, the carbonate ester, alkoxy alkyl carbonate ester, alkoxy alkyl ester, etc. prodrugs as disclosed in Formulae I, Ia, II, and IIa as R5, that is selected from groups consisting of H with R6, R7 and R8 substitutions. The present Application, WO'262 claims the same kind of prodrugs which are already disclosed in WO'257 at the

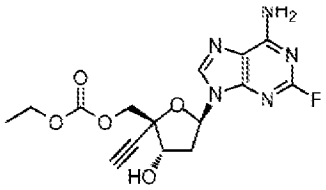
carbonate ester, alkoxy alkyl ester] Some of the Compounds exemplified in WO'257 are as listed herein below: **<u>Alkoxy alkyl ester</u>** <u>i.</u> Methoxy methyl isobutyrate (Compound 1, p.13)  **Alkoxy alkyl carbonate ester** i. Methoxy methyl isopropyl carbonate (Compound 2, p.13)  ii. Methoxy methyl decyl carbonate (Compound 6, p.14)  iii. Methoxy methyl hexadecyl carbonate (Compound 11, p.14) 	methyl esters with lower alkyl chains (C5, C6, C9, respectively) 2.Methyl palmitate (Example 16, p.65)  Similarly, Examples 87 (p.114), 90 (p.114), 91 (p.115) disclose methyl esters with higher alkyl chains (C14, C12, C20, respectively 3. Methyl decanoate (Example 20, p.68)  **Carbonate ester prodrugs** 1. Methyl pentyl carbonate (Example 14, p.64)  **2.** Methyl decyl carbonate (Example 18, p. 66) 	same position of the tetrahydrofuran ring. Thus, with respect to these prodrug moieties substituted at the 2-hydroxymethyl position of the tetrahydrofuran ring, the present Application, WO'262 lacks inventive step (to the extent of overlap).

Carbonate ester

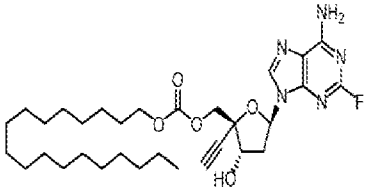
i. Methyl dodecyl carbonate (Compound 4, p.13)



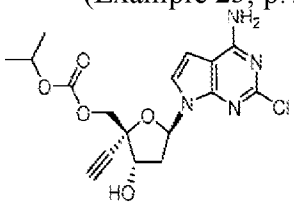
ii. Methyl ethyl carbonate (Compound 5, p.13)



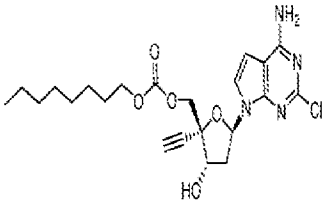
iii. Methyl octadecyl carbonate (Compound 13, p.14)



3. Methyl isopropyl carbonate (Example 23, p.72)



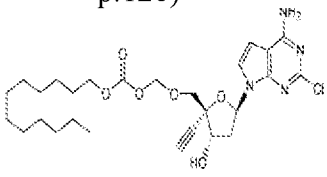
4. Methyl octyl carbonate (Example 39, p.82,

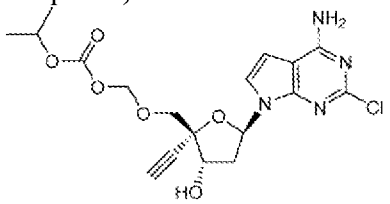
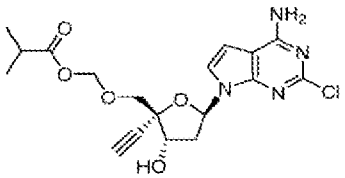


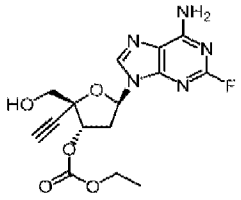
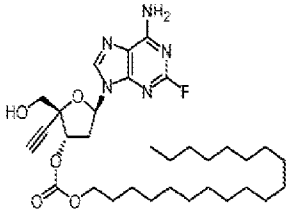
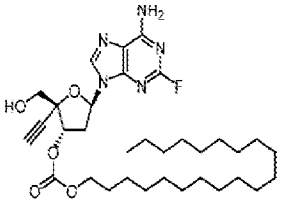
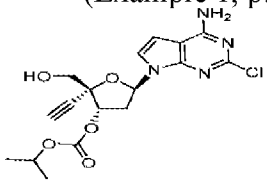
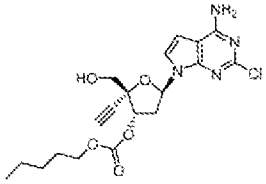
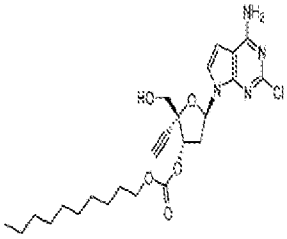
Similarly, Examples 112 (p.121), 117 (p.122), 120 (p.123), 121 (p.123), 126 (p.124) disclose methyl alkyl carbonate esters containing C8, C12, C6, C7, C9 alkyl chain respectively.

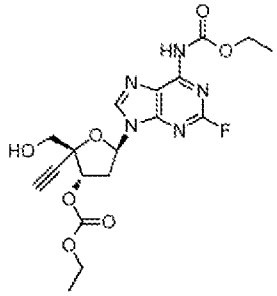
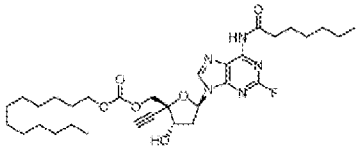
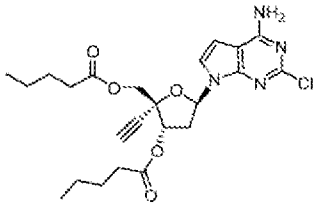
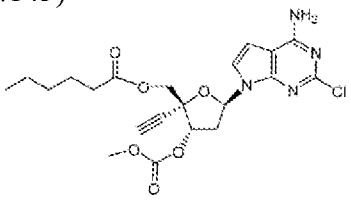
Alkoxy alkyl Carbonate ester prodrugs

1. Methoxy methyl dodecyl carbonate (Example 134, p.126)



	2. Methoxy methyl isopropyl carbonate (Example 133, p.126)  **<u>Alkoxy alkyl ester prodrugs</u>** 1. Methyl isobutyrate (Example 54, p. 92) 	
D. Prodrug substitutions at the 3rd position on the tetrahydrofuran ring in the prior art document, WO'257, and the present Application, WO'262		
WO'257 discloses Compound of Formulae I, Ia, II, IIa, wherein the substituent R3 at the 3-hydroxy position is selected from a group consisting of H, and -C(=O)-O-R4, wherein R4 is (C1-C25) alkyl or (C1–C6)alkyl. WO'257 exemplifies and claims compound wherein the prodrugs are explored at the 3-hydroxy position. Some of the compounds are listed herein below:	The present Application, WO'262, based on defining the variables X and R2, claims that the prodrug moieties explored at the 3rd position on the tetrahydrofuran ring includes ester, carbonate ester, etc, wherein X is selected from -C(=O), C(=O)-O; and R2 is selected from a group consisting of H, C1-12 alkyl, etc., which can be optionally substituted with one to three groups selected from C1-6 alkyl, etc.	As can be seen, the 3rd position on the tetrahydrofuran ring has been substituted in WO'257 with various prodrug moieties, that include the carbonate, etc. prodrugs, with various lengths of the alkyl chain, as disclosed in Formulae I, Ia, II, and IIa as R3, that is selected from groups consisting of H, C(=O)-O R4, wherein R4 is C1-C25 alkyl, wherein R3 is a

Carbonate Ester Prodrugs (i) Ethyl carbonate (Compound 8, p.14)  (ii) Nonadecyl carbonate (Compound 9, p.14)  (iii) Icosyl carbonate (Compound 10, p.14) 	**Carbonate ester prodrugs** 1. Isopropyl carbonate (Example 1, p.56)  2. Pentyl carbonate (Example 13, pp.63–64)  3. Decyl carbonate (Example 10, p.61)  Similarly, Examples 61 (p.96), 142 (p.129), 153 (p.132), etc disclose carbonate ester prodrugs containing C6, C5, C7 alkyl chain respectively.	prodrug – ester, carbonate, etc. with R6, R7 and R8 substitutions. The present Application, WO'262 uses the same kind of prodrugs already disclosed in WO'257 at the same position of the tetrahydrofuran ring. Thus, with respect to these prodrug moieties substituted at the 3rd position of the tetrahydrofuran ring, the present Application, WO'262 lacks inventive step (to the extent of overlap).

E. Prodrugs explored at multiple positions in a single compound		
WO'257 discloses that compounds of Formulae I, Ia, II, IIa can be derivatized at any of three positions described above, or at multiple of these positions. Some of the claimed and exemplified compounds show such multiple promoieties in a single compound, which are listed herein below 1. Ethyl carbamate at 4-amino position and ethyl carbonate ester at 3-hydroxy position (Example 7, pp.46–47)  2. Heptanamide at 4-amino position and methyl dodecyl carbonate ester at 2-hydroxymethyl position (Example 12, pp.52–53) 	The present Application claims compounds of Formulae I–VI, wherein prodrugs can be formed at any of the three positions as described above, or at multiple of these positions. Some of the claimed (Claims 10–11) and exemplifies compounds of WO'262, where promoieties are formed at multiple positions in a single compound are listed herein below. 1. Pentanoate at 3-hydroxy position, and pentanoyloxy methyl at 2-hydroxymethyl position on the THF ring (Example 7, pp.59–60)  2. Methyl carbonate ester at 3-hydroxy position, and methyl hexanoate at 2-hydroxymethyl position on the THF ring (Example 188, p.143)  Similarly Examples 92 (p.115), 146 (p.130), 185–189 (pp.141–142), 189 (p.143), etc also disclose prodrug formation at multiple positions; these promoieties comprising alkyl chains of varying chain lengths.	As can be seen, WO'257 claims and exemplifies compounds wherein prodrug formation has been explored at two of the three positions described above. The promoieties can be same or different. The present Application, WO'262 claims several compounds wherein the prodrug formation has been explored at two of the three positions, and wherein the promoieties are same or different. Thus, with respect to these compounds with multiple prodrug moieties substituted on the tetrahydrofuran ring and the pyrrolopyrimidine ring, the present Application,

		WO'262 lacks inventive step (to the extent of overlap).

Thus, WO'257 already discloses prodrugs at 4-amino position on nucleobase, and the 2 and 3 position on the THF ring, the prodrug categories including amide, carbamate, ester, carbonate ester, alkoxy alkyl carbonate ester, alkoxy alkyl ester, etc.

TABLE III: COMPARISON OF PRIOR ART WO 2021/021717 (WO'717) AND THE PRESENT APPLICATION WO 2024/163262 (WO'262)

The table below shows a comparison of the various prodrugs explored for EFdA in prior art document WO 2021/021717 and the prodrugs that are claimed for MK-8527 (a deaza analogue of EFdA) in the present Application, WO 2024/163262.

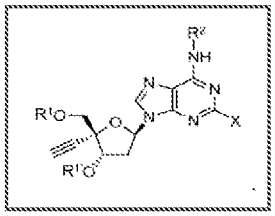
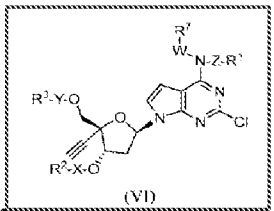
Table III		
Prior art WO 2021/021717	**Present Application WO 2024/163262**	**Comment**
An adenosine derivative having a formula (1), or pharmaceutically acceptable salt, stereoisomer, tautomer, or solvate thereof:  wherein, R^1, R1', and R^2 each is independently -H, - -C(O)OR^4, -R^5, -L1-R5, or -Z-L4-R5, wherein at least one of R1 and R2 is not -H;	A compound of Formula (VI):  (VI) or a pharmaceutically acceptable salt thereof, wherein: X is selected from -C(=O)-, -C(=O)-O-, -C$R^5$$R^6$-O-C(=O)-, -C$R^5$$R^6$-O-C(=O)-O-, and a bond; aryl Y is selected from -C(=O)-, -C(=O)-O-, -C$R^5$$R^6$-O-	WO 2021/021717 discloses carbonate ester prodrugs where R^1, $R^{1'}$ and R^2 is C(O)OR^4, and the terminal R^4 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl (such as adamantyl), 3-10 membered heterocycloalkyl, aryl, or heteroaryl (such as pyridyl). Similarly, the present Application, WO 2024/163262, claims carbonate esters of adenosine derivatives formed at the 3'- and 5'- positions of the sugar / tetrahydrofuran moiety or the 4-amino of the

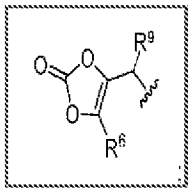
Table III		
Prior art WO 2021/021717	**Present Application WO 2024/163262**	**Comment**
R^3, $R^{3'}$ and R^4 each is independently -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3-10 membered heterocycloalkyl, aryl, or heteroaryl; *[Note: The cycloalkyl may be a fused or bridged ring systems having up to 20 C atoms, 3 to 10 carbon atoms, such as adamantyl), 3-to 10-membered heterocycloalkyl (fused or bridged ring systems), or heteroaryl (such as pyridyl) (pp.10–11)]* R5 is  R6 is -H, C1-C10 alkyl, C2-C10 alkenyl, C3-C10 cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, or heteroaryl -L1-R5 is … -C(O)O-R^5 … -Z is a divalent -C(O)-, -C(O)O-, etc;	C(=O)-, -CR^5R^6-O-C(=O)-O-, -P(=O)(O-C_{6-12} aryl)-NH-CR^4C(=O)-O-, and a bond: Z is selected from -C(=O)-, -C(=O)-O-, and a bond; W is selected from -C(=O)-, -C(=O)-O-, and a bond; R^1 is selected from the group consisting of hydrogen, C_{1-21} alkyl, $(CR^5R^6)_z$-C_{3-12}cycloalkyl, $(CR^5R^6)_z$-C_{5-12}heterocyclyl, $(CR^5R^6)_z$-C_{6-12} aryl, $(CR^5R^6)_z$-C_{5-12} heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with one to three groups independently selected from halo, C_{1-6} alkyl, C_{3-12} cycloalkyl and hydroxy: R^2 is selected from the group consisting of hydrogen, C_{1-21} alkyl, $(CR^5R^6)_z$-C_{3-12}cycloalkyl, $(CR^5R^6)_z$-C_{5-12}heterocyclyl, $(CR^5R^6)_z$-C_{6-12} aryl, $(CR^5R^6)_z$-C_{5-12} heteroaryl, and $(CR^5R^6)_z$-C_{1-6} alkyl ester, wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with one to three groups independently selected from halo, oxo, C_{1-6} alkyl, C_{3-12} cycloalkyl and hydroxy; R^3 is selected from the group consisting of hydrogen, C_{1-21} alkyl, $(CR^5R^6)_z$-C_{3-12}cycloalkyl,	nucleobase, i.e., when X, Y, W and Z is -C(=O)-O- respectively. In the present Application, WO 2024/163262, the carbonate ester is further substituted at the terminal end with hydrogen, alkyl or cycloalkyl (R1, R7 on the 4-amino and R2 or R3 at the 3'- and 5'- position of the sugar / tetrahydrofuran moiety) or with a heterocyclyl, aryl or heteroaryl (R7 on the 4-amino and R2 or R3 at the 3'- and 5'= position of the sugar/tetrahydrofuran moiety). However, WO 2021/021717 discloses such carbonate ester prodrugs including those with an ODOL moiety as well as a terminal adamantyl, cycloalkyl or heteroaryl moiety.

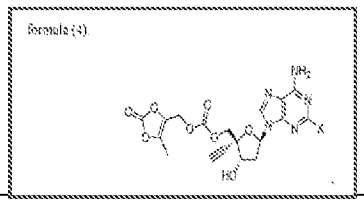
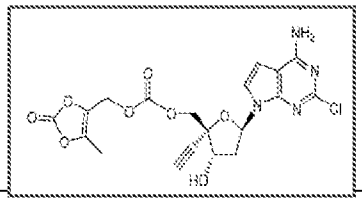
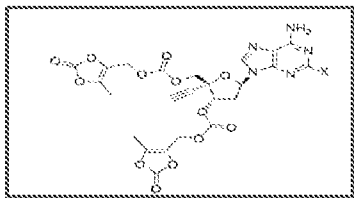
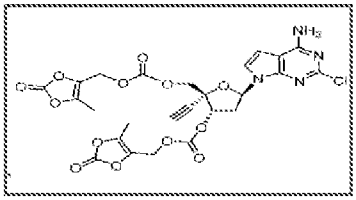
Table III		
Prior art WO 2021/021717	**Present Application WO 2024/163262**	**Comment**
R7, R 8 and R9 each is independently -H, C1-C 10 alkyl, etc; L2 and L3 each is intendedly divalent -(C1-C10 alkyl)-, or -(C2-C10 alkenyl)-; and X is a halogen atom (e.g., Cl)	$(CR^5R^6)_z$-C_{5-12}heterocyclyl, $(CR^5R^6)_z$-C_{6-12} aryl, and $(CR^5R^6)_z$-C_{5-12} heteroaryl wherein said alkyl, cycloalkyl, heterocyclyl, or heteroaryl group can be optionally substituted with one to three groups independently selected from halo, oxo, C_{1-6} alkyl, C_{3-12} cycloalkyl, or hydroxy, and wherein said aryl can be optionally substituted with one to three groups independently selected from halo, oxo, C_{1-6} alkyl, C_{3-12} cycloalkyl, hydroxy, and C_{1-6} alkyl ester: R^4 is selected from the group consisting of hydrogen, C_{1-3} alkyl and $(CH_2)_z$cycloalkyl; R^5 and R^6 are each independently selected from hydrogen, a halogen. C_{1-3} alkyl, and C_{3-6} cycloalkyl; and R^7 is selected from hydrogen, C_{1-21} alkyl and $(CR^5R^6)_z$-C_{5-12}cycloalkyl, wherein at least one of R^1, R^2 and R^3 is not hydrogen; and z is 0, 1, 2, 3, 4, 5, or 6.	
Some specific ODOL prodrugs of adenosine derivatives that are claimed in prior art document WO 2021/021717 and in the present Application, WO 2024/163262, are set out below.		
Claim 24: Formula (4) 	Claim 10, p. 186, Structure 2 	WO 2021/021717 discloses and claims an ODOL prodrug moiety at the 5'-position of the sugar moiety of an adenosine derivative. The present Application, WO 2024/163262, similarly

Table III		
Prior art WO 2021/021717	**Present Application WO 2024/163262**	**Comment**
		claims an ODOL prodrug moiety for an adenosine analogue.
Claim 24: Formula (4-B) 	Claim 10, p. 170, Row 3, structure 2 	WO 2021/021717 discloses and claims ODOL prodrug moieties at both the 3'- and 5'- position of the sugar moiety of the adenosine derivative. The present Application, WO 2024/163262, similarly claims ODOL prodrug moieties at the same two positions for an adenosine analogue.

Thus, WO'717 already discloses the carbonate ester prodrugs, including those with an ODOL moiety as well as a terminal adamantyl, cycloalkyl or heteroaryl moiety, of a adenosine analogue.

Further, WO2018133835 (WO'835) relates to nucleoside (preferably adenosine) analogues, including tubercidin (i.e., Compound 21, p.24 of WO835, substituted with 2-hydroxymethyl-3,4-dihydroxy), for modulating circadian rhythm (Abstract; pp.1, 5). Albeit for a different pharmacological indication, Compound 13 (p.2 of WO'835) is structurally similar to Compound of Example 145 (p.130 of WO'262), differing only in that the nucleobase in WO835 is adenosine, while that in WO'262 is an adenosine analogue (2-chloro-deaza-deoxyadenosine). It may be noted that the side chain of Compound 13 (also seen in compounds 8–12, 14–15) is the biotin molecule (5-[2-oxo-hexahydro-1H-thieno[3,4-d]imidazol-4-yl]pentanoic acid, which comprises a heterocycloalkyl moiety (fused bicyclic ring) attached to an alkyl chain). WO2015143712 [attached as Citation 1 in the accompanying TPO] already discloses Compounds of Formula II and prodrugs thereof, having HIV reverse transcriptase inhibitory activity; the prodrugs of

WO'712 including ester, carbonate ester, amide, carbamate, etc prodrugs having alkylene chain attached to a terminal cycloalkyl moiety. Hence, it is obvious to a person skilled in the art to explore the biotin side chain disclosed in WO'835 for a similar nucleoside analogue for HIV reverse transcriptase inhibitory activity.

C. VALIDITY OF THE CLAIMED PRIORITY DATE

The priority document filed on 30.01.2023, from which the present Application, WO'262, claims priority has only 17 claims. The Markush formula VI (Claim 1 of WO'262) (shown above in B.1 (1)), is neither claimed, nor disclosed in the priority document dated 30.01.2023. The variable W in the substituent at the 4-amino position of the pyrrolopyrimidine ring is not disclosed. Hence, those compounds of WO'262 which have 2 promoieties attached to the Nitrogen atom at the 4th position of the pyrrolopyrimidine ring, including Examples 217, 218, 220, 222, etc (pp.152–153; Claim 10 of WO'262) cannot validly claim the priority date of 30.01.2023.

Also, this first filed priority document only exemplifies and claims 59 compounds (disclosed in Table A of WO'262; pp.13–18 of WO'262).

It is only the second filed priority document, dated 08.12.2023 that discloses and claims all the aspects claimed in the present Application, WO'262.

Thus, the priority date for the claims relating to variable Won the pyrrolopyrimidine ring, and the di-substituted amide or carbamate prodrugs, as exemplified in the examples mentioned hereinabove, would be 08.12.2023, and **not** 30.1.2023.

D. CONCLUSION

Thus, as shown above, several prodrug moieties have been explored in the prior art for adenosine analogues (such as EFdA and its analogue MK-8527), including identical prodrug moieties (ester, carbonate ester, alkoxy alkyl carbonate ester, amide, carbamate, phosphoramidate, etc). These same prodrug moieties have been claimed in the present Application WO'262, for Compound A (i.e., MK-8527).

In light of the above and the documents cited in the accompanying TPO, Claims 1 to 22 of the present Application, WO'262, lack novelty, to the extent of overlap, and lack inventive step.