Third party Observations

Personal details

Name

1. Charitable Organisation “100 Percent Life”; 2.Public Association “Positive Initiative” (Asociația Obștească “Inițiativa Pozitivă”); 3.International Treatment Preparedness Coalition – Middle East and North Africa (ITPC MENA); 4. ATL MST/SIDA (Association Tunisienne de Lutte Contre les MST et le SIDA); 5. Foundation Salud por Derecho (Fundación Salud por Derecho)

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Subject

Application Number

24709908.8

Publication Number

EP4658663

Title

PRODRUGS OF 4'-SUBSTITUTED NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Observations

Upload document

Observations document

File attached

TIPA1.pdf

Facts and evidence

Patent literature

Patent literature 1

Publication Number

WO2015148746

Reference

D1

Title

4'-SUBSTITUTED NUCLEOSIDE-DERIVATIVES AS HIV REVERSE TRANSCRIPTASE INHIBITORS

Date of Publication

2015-10-01

File attached

WO_2015148746_A1.pdf

Patent literature 2

Publication Number

US2019185508

Reference

D2

Title

DEUTERATED NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Date of Publication

2019-06-20

File attached

US_2019185508_A1.pdf

Patent literature 3

Publication Number

WO2020178767

Reference

D3

Title

COMPOUNDS USEFUL IN HIV THERAPY

Date of Publication

2020-09-10

File attached

WO_2020178767_A1.pdf

Patent literature 4

Publication Number

WO2021021717

Reference

D5

Title

ADENOSINE DERIVATIVE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

Date of Publication

2021-02-04

File attached

WO_2021021717_A1.pdf

Patent literature 5

Publication Number

WO2021188959A

Reference

D4

Title

PRODRUGS OF 4'-C-SUBSTITUTED-2-HALO-2'-DEOXYADENOSINE NUCLEOSIDES AND METHODS OF MAKING AND USING THE SAME

Date of Publication

2021-09-23T00:00:00.000+03:00

File attached

WO_2021188959_A1.pdf

Patent literature 6

Publication Number

WO2022159872

Reference

D6

Title

ADENOSINE DERIVATIVE AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

Date of Publication

2022-07-28

File attached

WO_2022159872_A1.pdf

Patent literature 7

Publication Number

WO2020086555

Reference

D8

Title

ANTIVIRAL PRODRUGS AND NANOFORMULATIONS THEREOF

Date of Publication

2020-04-30

File attached

WO_2020086555_A1.pdf

Patent literature 8

Publication Number

US20200239513

Reference

D9

Title

Long-acting prodrugs of entecavir, preparing methods and uses thereof

Date of Publication

2020-07-30T00:00:00.000+03:00

File attached

US_2020239513_A1.pdf

Non-Patent literature

Non-Patent literature 1

Reference

D7

Title

Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs

Author

Pradere U, Garnier-Amblard EC, Coats SJ, Amblard F, Schinazi RF

Date of Publication

21.08.2014

File attached

cr5002035.pdf

To the European Patent Office

Third-party observations under Article 115 EPC
For European patent application 24709908.8 with the following details:

Publication date	10.12.2025
EP application number / publication number	EP 24709908.8 / EP 4658663 A2
International application number (PCT)	PCT/US2024/013021
International filing date	26.01.2024
Title	Prodrugs of 4'-substituted nucleoside reverse transcriptase inhibitors
Priority date	30.01.2023
Applicant	Merck Sharp & Dohme

Dear Sirs and Madams,

With this letter and below - mentioned evidences we want to object against the patentability of European patent application 24709908.8 under Article 115 EPC.

The grounds, which are described in details below, are lack of inventive step under Article 56 EPC, exclusion from patentability under Article 53(c) EPC, insufficiency of disclosure under Article 83 EPC, lack of clarity and support under Article 84 EPC, and lack of unity of invention under Article 82 EPC and Rule 44(1) EPC.

1. INTRODUCTION

The compound MK-8527 ((2R,3S,5R)-5-(4-amino-2-chloropyrrolo[2,3-d]pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)oxolan-3-ol)[1] is an HIV nucleoside reverse transcriptase translocation inhibitor (NRTTI), characterized as a **7-deaza-2'-deoxyadenosine analog**. MK-8527 has a structure and inhibitory mechanism similar to islatravir (Figure 1). Both structures are derived from adenosine nucleotide (adenine + ribose sugar), MK-8527 differs from islatravir by a modification of the nucleobase: a reduction in the number of ring nitrogens (three instead of four) and a change in the halogen substituent from fluorine to chlorine. Unlike its predecessor, MK-8527 is

[1] In this patent application, MK-8527 is referred as (2R,3S,5R)-5-(4-amino-2-chloro-7H-pyrrolo[2,3-d] pyrimidin-7-yl)-2-ethynyl-2-(hydroxymethyl)tetrahydrofuran-3-ol (compound 4).

expected to maintain a favorable safety profile regarding lymphocyte counts[2]. The compound was reported to bear long intracellular half-lives, supporting extended-duration dosing intervals, due to the halogenation (chlorine) at the adenine ring which confers resistance to degradation by the enzyme adenosine deaminase, resulting in an increase in the half-life ($T_{1/2}$) of the compound[3].

Currently, MK-8527 is undergoing evaluation in **phase 3 clinical trial**, which investigates its efficacy, safety and tolerability of **once-monthly oral** Pre-Exposure Prophylaxis (PrEP) candidate compared to daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) in sexually active people across 16 countries (EXPrESSIVE-11, NCT07044297[4]) and in sexually active women aged 16 to 30 in some African countries[5] (EXPrESSIVE-10, NCT07071623[6])[7].

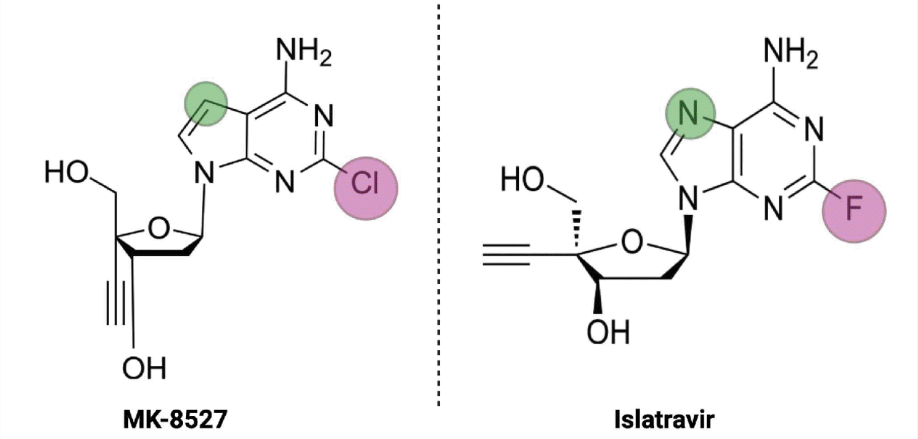


Figure 1. Comparison between the structural representations of MK-8527 and islatravir. Differences in the structures are labeled in green (-CH instead of -N, respectively) and purple (-Cl instead of -F, respectively).

2. CLAIMS (Annex)

[2] Safety and pharmacokinetics of MK-8527 oral once-monthly: a phase 2 study in adults at low risk of HIV-1 exposure, oral. IAS 2025, 13th IAS Conference on HIV, 2025. Available at: https://www.natap.org/2025/IAS/IAS_36.htm

[3] Raheem IT, Girijavallabhan V, Fillgrove KL, Goh SL, Bahnck-Teets C, Huang Q, Li F, Wan B-L, O'Donnell GT, Patteson JB, Cilento ME, Bennet A, Hayes RP, Tummala S, McHale C, Wiltsie J, Ellis J, Asante-Appiah E, Hazuda DJ, Hale J, Grobler JA, Xu M, Diamond TL, Lai M-T. MK-8527 is a novel inhibitor of HIV-1 reverse transcriptase translocation with potential for extended-duration dosing. PLoS Biol 23(8): e3003308, 2025. Available at: https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3003308

[4] Available at: https://clinicaltrials.gov/study/NCT07044297?intr=MK-8527&limit=25&page=1&rank=11

[5] The company plans included the countries Kenya, South Africa and Uganda, but just South Africa is included yet.

[6] Available at: https://clinicaltrials.gov/study/NCT07071623?intr=MK-8527&limit=25&page=1&rank=12

[7] Available at: https://www.merck.com/news/merck-to-initiate-phase-3-trials-for-investigational-once-monthly-hiv-prevention-pill/

3. SYNTHESIS OF THE CLAIMS

TYPE OF PROTECTION	CLAIMS	DETAILS
Compound	1-11	Markush Formulas I, II, III, IV, V and VI (claims 1-9); 227 selected compounds (claim 10); 14 selected compounds (claim 11) or a pharmaceutically acceptable salt thereof.
Composition	12-14	Pharmaceutical composition comprising an effective amount of any compound of claims 1-11 or a salt and a vehicle (claim 12), for injection (claim 13), further comprising additional therapeutic agents (claim 14).
Method of treatment	15-20	Method for the treatment or prophylaxis of HIV infection (claim 15), or delaying the onset or progression of AIDS in a subject (claim 16), comprising administering an effective amount of any of the compounds of claims 1-11, their salts or pharmaceutical composition (claim 16), with additional therapeutic agents (claims 17-18), at a dosing interval of approximately once a month to approximately once every twelve months (claims 19-20).
Compound for use	21-22	Compound of any of claims 1-11 for use in the preparation of a medicament for the inhibition of HIV reverse transcriptase for the treatment or prophylaxis of HIV (claim 21), for use in therapy (claim 22).

4. PATENT FILING FOR MK-8527 THROUGH THE PCT SYSTEM

International publication number (WO/PCT)	Main content
WO/2015/143712 PCT/CN2014/074294	Markush formulas and selected compounds
WO/2015/148746 PCT/US2015/022621	Markush formulas and selected compounds

International publication number (WO/PCT)	Main content
WO/2017/053216 PCT/US2016/052409	Process and intermediates to prepare
WO/2024/163262 PCT/US2024/013021	**Prodrugs of MK-8527**

The patent application relevant to the present third-party observations is indicated **in bold.**

5. FIELD OF THE INVENTION

"[0005] The present invention is directed to prodrugs of 4'-substituted nucleoside derivatives and their use in the inhibition of HIV reverse transcriptase. The present invention is further directed to the use of these compounds in the prophylaxis of infection by HIV, the treatment of infection by HIV, and the prophylaxis, treatment, and delay in the onset or progression of AIDS and/or ARC, in a subject in need thereof. The present invention provides compounds that are solubility-limiting, cleavable prodrugs of NRTIs that may be adapted for extended dosing regimens for a subject in need thereof." (present patent application, page 2, description)

6. TECHNICAL PROBLEMS

"(...) a need to develop additional HIV antiviral drugs including additional reverse transcriptase (RT) inhibitors. A particular problem is the development of active RT inhibitors that are adapted for extended dosing, or sustained release regimens. There remains a significant need for improved treatment and prevention of HIV infections using long-acting RT inhibitors." (present patent application, pages 1-2, description)

7. PRIOR ART

D1: WO2015148746. 4'-Substituted nucleoside-derivatives as HIV reverse transcriptase inhibitors. Publication date: 01/10/2015. Applicant: Merck Sharp & Dohme.

D1, cited in this application, refers to the second patent application related to compound MK-8527 (the other application being WO2015143712). **D1** discloses 4'-substituted nucleoside derivatives of Formula I and, more particularly, 4'-ethynyl-2'-deoxynucleosides. **D1** discloses 23 specific compounds and their anti-HIV inhibitory effect. **D1** also discloses any prodrug thereof that is converted in vivo to the corresponding 4'-substituted nucleoside derivative or the corresponding 5'-triphosphate nucleoside of Formula I.

D2: US2019185508. Deuterated nucleoside reverse transcriptase inhibitors. Publication date: 20/06/2019. Applicant: Merck Sharp & Dohme and Idenix Pharmaceuticals.

D2 discloses deuterated derivatives of known 4'-ethynyl nucleoside derivatives from D1 (WO2015148746) and their use in HIV reverse transcriptase inhibition, as well as prodrugs thereof. In **D2**, the applicant selects two specific compounds for derivatization with deuterium.

D3: WO2020178767. Compounds useful in HIV therapy. Publication date: 10/09/2020. Applicant: GlaxoSmithKline and ViiV Healthcare.

D3 discloses various modifications of prodrugs of 4'-C-ethynyl-(2-halo)- 2'-deoxyadenosine, a reverse transcriptase inhibitor, for use in the treatment of HIV infection. The main difference between many of the compounds disclosed here and the compounds in this application lies in the nucleobase structure.

D4: WO2021188959. Prodrugs of 4'-C-substituted-2-halo-2'-deoxyadenosine nucleosides and methods of making and using the same. Publication date: 23/09/2021. Applicant: Gilead Sciences.

D4 discloses various modifications of prodrugs of 4'-C-ethynyl-(2-halo)- 2'-deoxyadenosine, a reverse transcriptase inhibitor, for use in the treatment of HIV infection. The main difference between many of the compounds disclosed here and the compounds in this application lies in the nucleobase structure.

D5: WO2021021717. Adenosine derivative and pharmaceutical composition comprising the same. Publication date: 04/02/2021. Applicant: BRII Biosciences.

D5 discloses various modifications of prodrugs of 4'-C-ethynyl-(2-halo)- 2'-deoxyadenosine, a reverse transcriptase inhibitor, for use in the treatment of HIV infection. The main difference between many of the compounds disclosed here and the compounds in this application lies in the nucleobase structure.

D6: WO2022159872. Adenosine derivative and pharmaceutical composition comprising the same. Publication date: 28/07/2022. Applicant: BRII Biosciences.

D6 discloses various modifications of prodrugs of 4'-C-ethynyl-(2-halo)- 2'-deoxyadenosine, a reverse transcriptase inhibitor, for use in the treatment of HIV infection. The main difference between many of the compounds disclosed here and the compounds in this application lies in the nucleobase structure.

D7: Pradere U, Garnier-Amblard EC, Coats SJ, Amblard F, Schinazi RF. Synthesis of Nucleoside Phosphate and Phosphonate Prodrugs. Chemical Reviews, 114(18): 9154-9218, 2014.

D7 is a chemical review of mono-, di- and triphosphate nucleoside prodrugs, and particularly describes aryloxy phosphoramidate nucleotide prodrugs, called "ProTides" or "McGuigan" prodrugs, which lead to the intracellular release of the corresponding active nucleoside monophosphates.

D8: WO2020086555. Antiviral prodrugs and nanoformulations thereof. Publication date: 30/04/2020. Applicant: Board of Regents of the University of Nebraska (inventors: Gendelman HE, Edagwa BJ).

D8 discloses prodrugs of HIV integrase inhibitors (cabotegravir, raltegravir, elvitegravir, dolutegravir, bictegravir), wherein a hydroxyl group of the parent drug is replaced by an ester comprising a long-chain aliphatic/fatty-acid moiety (C14-C22), and nanocrystal formulations thereof, expressly for the purpose of obtaining long-acting, slow-release ("LASER ART") intramuscular depot formulations allowing dosing intervals of up to six months or longer. D8 is unrelated to D1-D7 (different applicant, different drug class) and demonstrates that the general strategy of converting a known anti-HIV drug into a long-acting ester prodrug was, independently of the NRTTI field, part of the common general knowledge well before the priority date of the present application.

D9: US2020/0239513. Long-acting prodrugs of entecavir, preparing methods and uses thereof. Publication date: 30/07/2020 (priority 29/09/2017). Applicant: Guangzhou Henovcom Bioscience Co., Ltd.

D9 discloses prodrugs of entecavir, a guanosine nucleoside analogue used in the treatment of hepatitis B virus infection, in which the free hydroxy group of entecavir is esterified with a long-chain fatty acid (e.g., the 5'-docosanoate, C22) or related acyl moiety, expressly for the purpose of obtaining sustained, long-acting intramuscular injectable suspensions. D9 is unrelated to D1-D8 (different applicant, different nucleoside, different indication) and confirms that ester-type, long-chain-acyl prodrug modification of a nucleoside analogue, specifically for the purpose of achieving a long-acting parenteral depot effect, was a generic and well-known strategy in nucleoside antiviral drug design, independent of the specific NRTTI/HIV context of the present application.

8. GROUNDS FOR THE THIRD-PARTY OBSERVATIONS

8.1 Lack of inventive step – Claims 1–22

8.1.1 Markush formulas and selected compounds – Claims 1–11

Claims 1-11 of this application relate to Markush Formulas I, II, III, IV, V, and VI (claims 1-9); 227 selected compounds derived from the Markush Formulas (claim 10); 14 selected compounds (claim 11); or a pharmaceutically acceptable salt thereof.

For the assessment of inventive step, **D1** is considered the closest prior art (specifically compounds 4 and 16). **D1** (WO2015148746) discloses 4'-substituted nucleoside derivatives derived from Formula I as HIV reverse transcriptase inhibitors (claim 1), and more particularly 4'-ethynyl-2'-deoxynucleosides (claim 16). Among the various compounds derived from Formula I, **D1** discloses 23 specific compounds and their anti-HIV inhibitory effect (Tables 2-4, pages 103-111), including compound 4 (referred to as compound (A) in this application) and its triphosphate derivative, compound 16. The structures of compounds 4 and 16 can be seen in Figure 2.

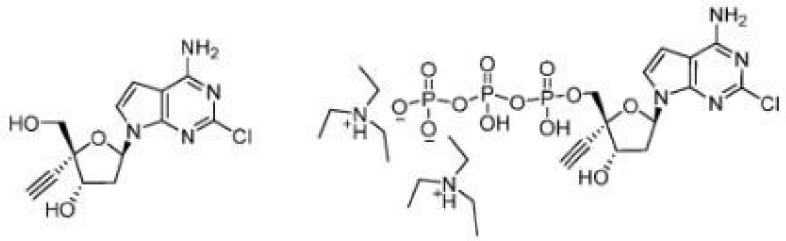


Figure 2: Compounds 4 (pages 47, 106, 109, and 114) and 16 (pages 83, 85, and 103), respectively, from **D1**

D1 (pages 17-19) also discloses any prodrug thereof that is converted *in vivo* to the corresponding 4'-substituted nucleoside derivative or the corresponding 5'-triphosphate nucleoside derivative of Formula I. Such prodrug modification groups include, for example, derivatives of a hydroxy group, such as an ester (-OC(O)R), a carbonate ester (-OC(O)(OR), or an ether (-OR), or mono-, di-, or triphosphate prodrugs, including phosphate esters, phosphoramidates ("McGuigan" or "ProTide" type prodrugs), SATE prodrugs, or cyclic phosphate esters; and when the derivative of the 4'-substituted nucleoside incorporates an amine functional group (as in compounds 4 and 16), its prodrug modification groups encompass several types of groupings.

"Prodrugs of compounds of Formula I can exhibit enhanced solubility, absorption, and/or lipophilicity compared to the compounds per se, thereby resulting in increased bioavailability and efficacy. When the compound contains, for example, a hydroxy group, the prodrug can be a derivative of the hydroxy group such as an ester (-OC(O)R), a carbonate ester (-OC(O)OR), a phosphate ester (-O-P(=O)$(OH)_2$), an ether (-OR), or a mono-phosphate prodrug such as a phosphoramidate (can be converted *in vivo* to the corresponding nucleoside monophosphate).

For example, if a compound of Formula I contains an alcohol functional group, a prodrug can be formed by the replacement of one or more of the hydrogen atoms of the alcohol groups with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl- 1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkyl, α-amino(C_1-C_4)alkylene-aryl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

The term "pro-drug modification of the mono-, di- or triphosphate" as used herein includes, but is not limited to, 5'-alcohol-derived prodrugs such as -P(O)(-O-C1-C6alkyl)$_2$; -P(O)(-NH-(a-aminoacyl group))(-O-aryl), known as "McGuigan" type prodrugs; -P(O)(-O-(C_1-C_6 alkylene)-S-acyl)(-NH-arylalkyl); S-acyl-2-thioethyl

(SATE) prodrugs; a cyclic phosphate ester that forms a bridge between two ribose hydroxyl groups (...)
(...)

If a 4'-substituted derivative incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl-, RO-carbonyl-, NRR'-carbonyl- wherein R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, a natural α-aminoacyl, -C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, -C(OY^2)Y^3 wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl; carboxy (C_1-C_6)alkyl; amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl; -C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N- or di-N,N-(C_1-C_6)alkylamino morpholino; piperidin-1-yl or pyrrolidin-1 -yl, and the like." (**D1**, pages 17-18, highlights ours)

D2 discloses deuterated derivatives of the known 4'-ethynyl nucleoside derivatives from D1 (WO2015148746) and their use in the inhibition of HIV reverse transcriptase, as well as prodrugs thereof. **D2** covers the same prodrug modifications as those covered in D1. Specifically, in **D2**, the applicant selects two specific compounds from the Formula I derivatives of D1 (compounds 2 and 4) for derivatization with deuterium.

D3 (ViiV Healthcare / GlaxoSmithKline) discloses, for islatravir (EFdA, 4'-C-ethynyl-2-fluoro-2'-deoxyadenosine), the same combination of 5'-carbonate and 3'-ester (or 5'-ester and 3'-ester) prodrug modifications now claimed in the present application, including straight-chain alkanoyl esters of varying chain length (e.g., hexanoyl, octanoyl, decanoyl), aryl-acetate esters and mixed carbonate/ester combinations (D3, pages 164 and 181-188), expressly for the stated purpose of obtaining a long-acting parenteral depot. Since islatravir and compound (A) are produced by the same general synthetic route from the same 4'-ethynyl nucleoside core and differ only in the identity of the nucleobase (2-fluoro-purine versus 2-chloro-7-deazapurine), a skilled person seeking a long-acting prodrug of compound (A) would have looked directly to **D3** as a direct template, and would have had every reasonable expectation of success in transposing its prodrug substituents onto compound (A).

D4 (Gilead Sciences), filed by yet another competitor, discloses prodrugs of the same 4'-C-substituted-2-halo-2'-deoxyadenosine nucleoside class bearing isobutyrate diesters at the 3'- and 5'-positions, structurally matching compound 42 of the present application (D4, page 43), and expressly states that "the compound of the present disclosure may also be used in the form of a prodrug or other suitably modified form that releases the active ingredient *in vivo*" (D4, page 51). The fact that two of the world's leading antiretroviral developers (ViiV/GSK in **D3** and Gilead in **D4**) independently arrived at materially the same ester-prodrug substituents for the same nucleoside scaffold, working entirely independently of **D1**, is itself compelling evidence of obviousness.

D5 and **D6** (BRII Biosciences), a third and entirely independent competitor unrelated to Merck, ViiV/GSK or Gilead, discloses the same 4'-C-ethynyl-(2-halo)-2'-deoxyadenosine prodrug class with, inter alia, an adamantyl-ethyl carbonate substituent (D6, page 93) that is structurally near-identical to compound 36 of the present application, differing only in the nucleobase. The corresponding granted United States family member of **D5/D6** expressly claims this adamantyl substituent as one of only a handful of explicitly enumerated R-group options, confirming that this is not a one-off disclosure buried in a long list, but a substituent the BRII inventors considered to be among the most relevant embodiments of their own invention. With three independent industry players (D3, D4, and D5/D6) having each, separately, selected materially the same narrow set of ester/carbonate substituents for materially the same nucleoside scaffold, the present application's claim 1-11 selection cannot represent an inventive contribution: it is, at most, the fourth instance of the same obvious design choice.

D7 is a review article that analyzes various mono-, di-, and triphosphate nucleoside prodrugs, and specifically describes aryloxy phosphoramidate nucleotide prodrugs, called "ProTides" or "McGuigan" prodrugs (named after Christopher McGuigan and his team, who explored the strategy around 1990), which lead to the intracellular release of the corresponding active nucleoside monophosphates. In particular, some examples of ProTides nucleosides in clinical trials at that time or approved by the FDA are detailed in **D7** (Figure 3).

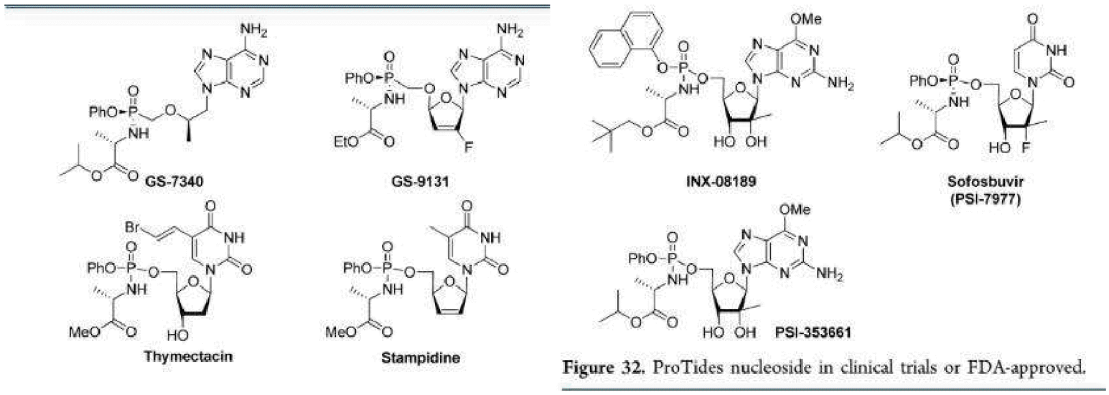


Figure 3: ProTides nucleosides exemplified in D7 (D7, Figure 32, section 3.3.1, page 9186).

The relevance of **D7** extends beyond the specific compounds discussed herein. It confirms that phosphoramidate ("ProTide") and related nucleotide prodrug technologies had become a part of the common general knowledge of the skilled person and represent established tools routinely employed to improve the pharmacokinetic profile of nucleoside analogues.

D8 discloses the same general strategy, which demonstrates, that the replacement of a free hydroxy group of a known anti-HIV drug with a long-chain ester

to obtain a long-acting, slow-release parenteral depot was applied to an entirely different class of anti-HIV agents (integrase inhibitors, independently).

D9 confirms that this same ester-type long-chain-acyl prodrug strategy was likewise applied to an unrelated nucleoside analogue (entecavir, used in hepatitis B treatment), again independently of **D1-D7** and of the NRTTI field.

Taken together, **D8** and **D9** demonstrate that the prodrug derivatisation strategy relied upon in the present application was not a contribution specific to compound (A) or to HIV reverse transcriptase inhibitors, but a generic technique known from the prior art, already employed across unrelated drug classes for the same purpose before the priority date.

For the evaluation of inventive step, **D1** is the closest prior art (specifically compounds 4 and 16). The difference between **D1** and the present patent application is the mandatory presence of at least one "prodrug-type modification group" in compounds 4 or 16 of **D1**, achieved by substituting at least one of the hydrogen atoms of the 3'- or 5'-hydroxy groups of the ribose or the 6-amino group of the nucleobase in compound 4, or by substituting at least one of the hydrogen atoms of the 3'-hydroxy group of the ribose or the 6-amino group of the nucleobase and/or by prodrug-type modification of the triphosphate group in compound 16.

The subject matter of the present patent application consists of a selection of the compounds described in **D1** for the same use, as reverse transcriptase inhibitors in the treatment of HIV infection.

Importantly, the present application neither identifies a different therapeutic target nor proposes a different pharmacological mechanism. The claimed compounds continue to function as prodrugs of the same class of HIV reverse transcriptase inhibitors and pursue the same objective already established in the prior art, namely optimisation of pharmacokinetic performance through conventional prodrug derivatisation.

The applicant only details water solubility tests (pages 160-162, description) for the 227 selected compounds, most of which have a solubility of less than 100 µg/mL. Furthermore, *in vitro* plasma stability tests (page 165) are performed for only 18 of the 227 compounds. Finally, *in vitro* metabolic stability tests (page 166) and the single *in vivo* plasma exposure test, in rats, are performed for only 14 of the 227 compounds (page 167 and Figures 1-15, comparison of compound A vs. 14 prodrugs of compound A). In the single *in vivo* assay, the 14 prodrugs tested (examples 10, 18, 20, 21, 24, 27, 34, 36, 42, 48, 60, 61, 64, and 68) had a similar half-life-extending effect of the compound between 4 and 7 days (Figures 2-15, approximately 0.1 µM of compound A around days 5-7).

Furthermore, the experimental evidence remains limited to a relatively small subset of the claimed compounds. While certain individual embodiments may exhibit the reported pharmacokinetic properties, the application does not establish that the

alleged advantages are achieved across substantially the entire scope of claims 1-11. Consequently, the available data cannot support the existence of a technical effect extending across the full breadth of the claimed genus.

The prodrugs of known compounds 4 and 16 of **D1**, as claimed, are obvious to a person skilled in the art. Starting with compounds 4 and 16 of **D1**, and to provide prodrugs thereof, a person skilled in the art would consider introducing the prodrug modifications suggested in **D1** and **D2** or in any of documents **D3-D9**, which are known to provide the same advantages and expected *in vivo* effects as those disclosed in this application, and thus arrive at the claimed compounds. Some disclosed examples:

> "Accordingly, prodrugs of the compounds of the invention are contemplated herein. A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term "prodrug" herein means a compound (e.g., a drug precursor), which may be in the form of a pharmaceutically acceptable salt, that is transformed intracellularly/in vivo to provide a 4' -substituted Nucleoside Derivative which is an inhibitor of HN reverse transcriptase. A nucleoside 5'triphosphate is an example of a 4'-substituted Nucleoside Derivative. The *in vivo* transformation may occur by various mechanisms, e.g., an enzyme-catalyzed chemical reaction, a metabolic chemical reaction, and/or a spontaneous chemical reaction (e.g., solvolysis), such as, for example, through hydrolysis in blood. This invention encompasses any prodrugs which convert, due to intracellular/in vivo conversion, to a 4' -substituted Nucleoside Derivative of a compound of Formula I which is an inhibitor of HIV reverse transcriptase. (...)" (**D1**, description, page 17, highlights ours).

> "The compounds of the present invention may be administered as prodrugs. Thus, certain derivatives of compounds of Formula (I), (Ia), (II) or (IIa), which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of Formula (I), (Ia), (II) or (IIa) as 'prodrugs'. One example of a compound that such prodrugs may encompass is 4'-ethylnyl-2-fluoro-2'-dooxyadenosine (EFdA).
> (...)
> The prodrugs are useful in that they are capable of modulating physicochemical properties, facilitating multiple dosing paradigms and improving pharmacokinetic and/or pharmacodynamic profiles of the active parent (EfdA). For example, the prodrugs may facilitate long-acting parenteral dosing modalities, and/or improvements in antiviral persistence profiles as compared to EFdA" (**D3**, description, page 42, highlights ours).

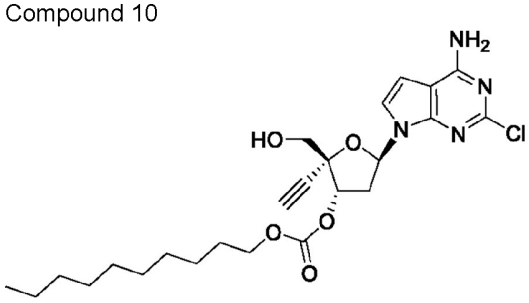
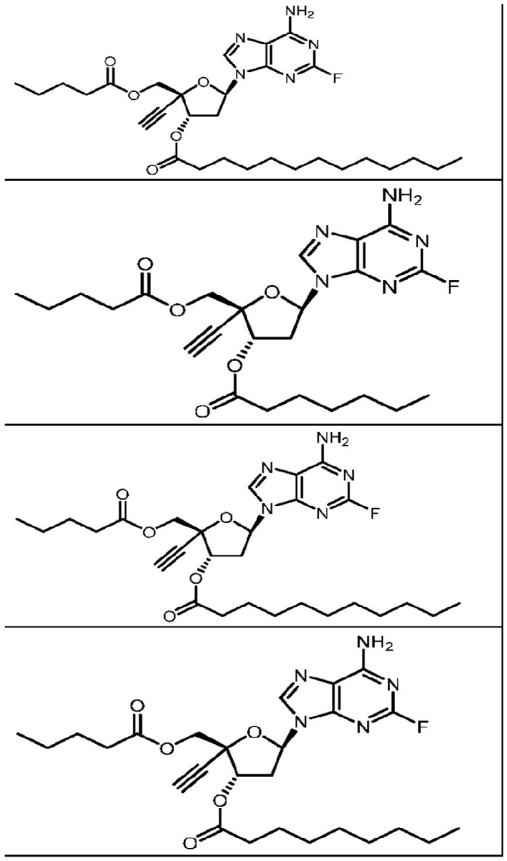
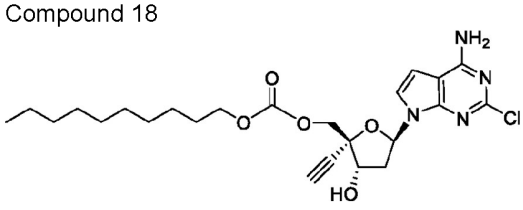
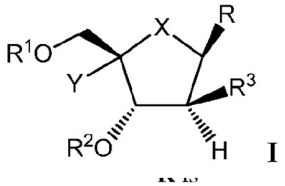
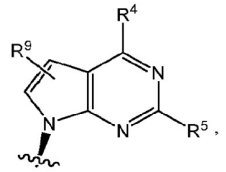
"[0115] The compound of the present disclosure may also be used in the form of a prodrug or other suitably modified form that releases the active ingredient *in vivo*." (**D4**, description, page 51, highlights ours).

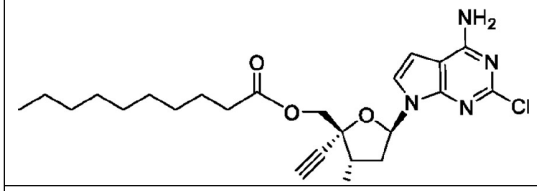
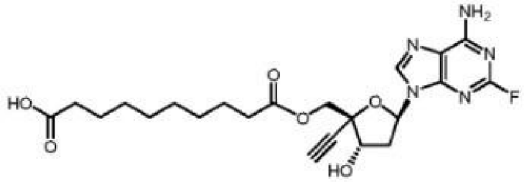
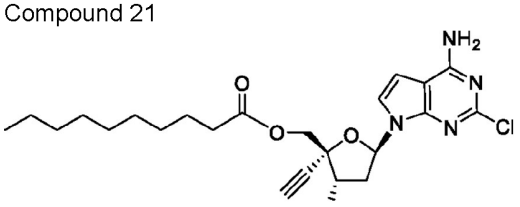
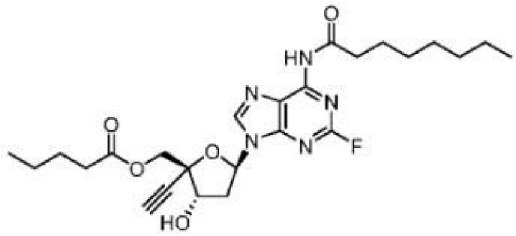
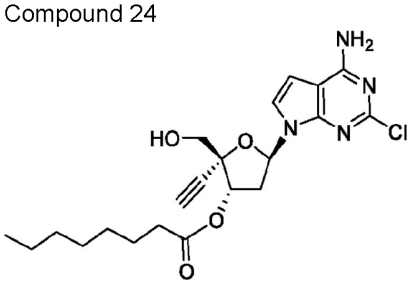
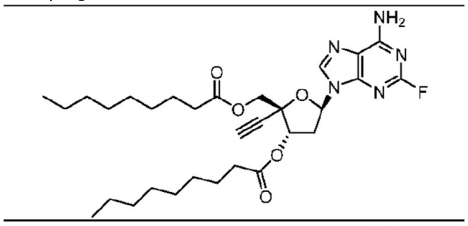
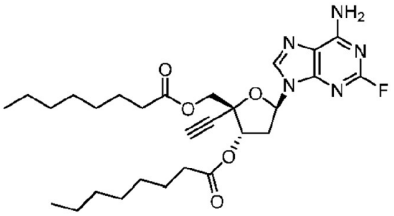
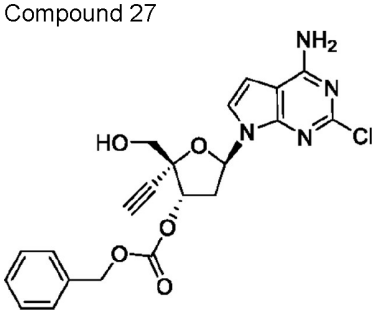
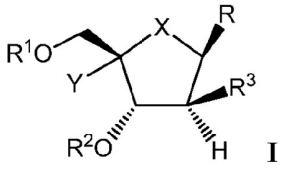
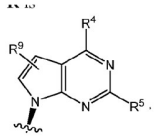
"[00040] The term "prodrug" refers to a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be a biologically inactive or substantially inactive compound which can be metabolized in the body, i.e., in vivo, to produce a drug having a desired activity. The term "substantially inactive" means that a prodrug can have about 1% to about 10% of the activity of the corresponding drug or after being metabolized in vivo, percentage based on weight of the prodrug. In some embodiments, the term "substantially inactive" means that a prodrug has less than about 5% of the activity of the corresponding drug or after being metabolized in vivo, percentage based on weight of the prodrug. The doses for a prodrug and its biologically active compound are considered to be dose-equivalent when they are the same molar amount." (**D5**, description, page 15, highlights ours).

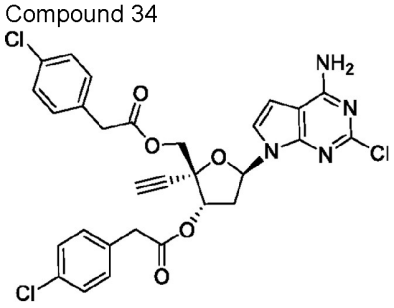
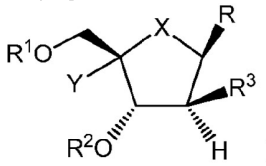
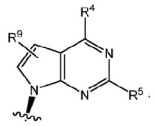
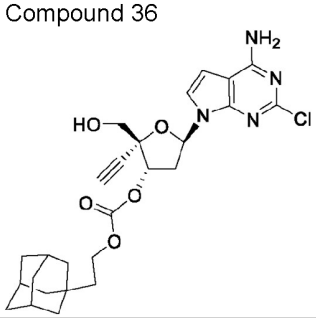
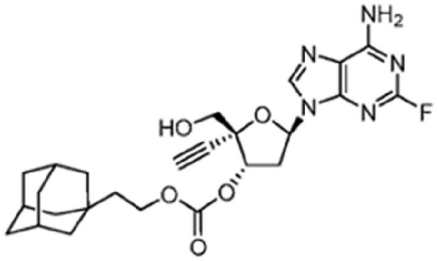
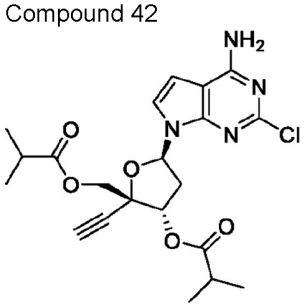
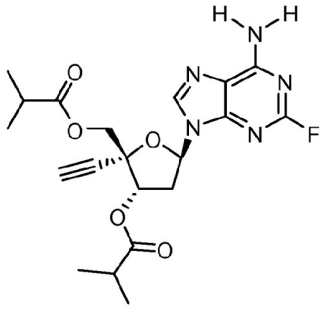
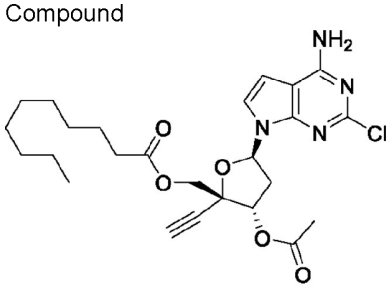
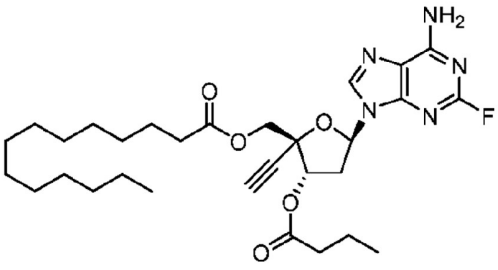
The existence of closely corresponding prodrug structures disclosed in multiple independent patent families substantially narrows the range of technical alternatives available to the person skilled in the art. Consequently, the presently claimed compounds cannot reasonably be regarded as the result of inventive selection from an unlimited range of possibilities, but rather as predictable embodiments falling within an already established technical feature.

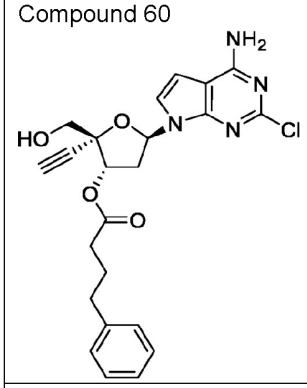
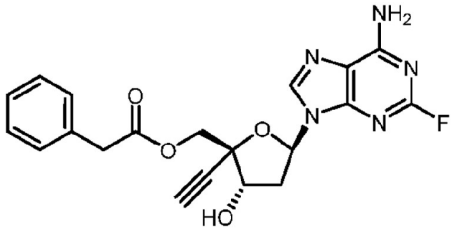
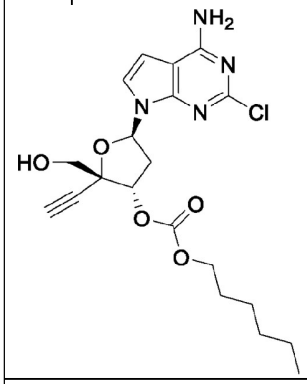
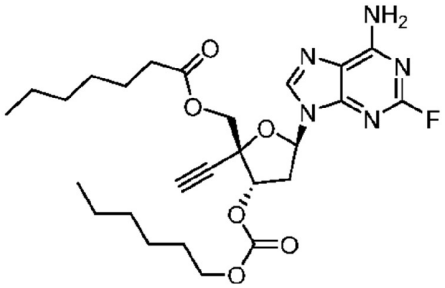
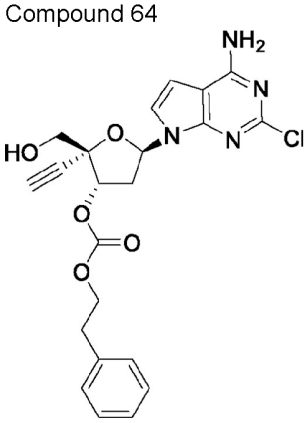
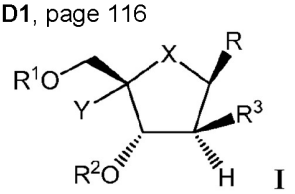
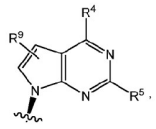
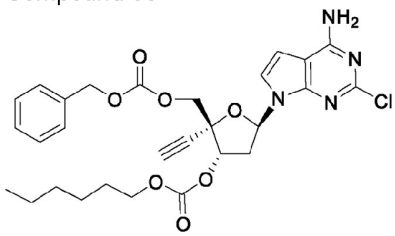
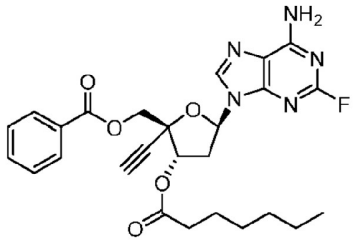
Furthermore, several prodrug modification structures claimed in the present application have already been disclosed in the prior art. Table 1 compares selected compounds from the present application (Examples 10, 18, 20, 21, 24, 27, 34, 36, 42, 48, 60, 61, 64, and 68) with corresponding compounds disclosed in **D1, D3, D4**, and **D6.** Although the compounds differ in their nucleobase structures, they incorporate the same or closely related prodrug modifications. In some cases, the prodrug modifications are identical (e.g., compound 36 and the compound disclosed in **D6,** page 93), whereas in others, they differ only in minor structural features, such as the number of carbon atoms in the ester carbon chain. In addition, generic disclosures corresponding to some of the claimed compounds were identified in Markush formulas of **D1**.

Table 1. Comparison between selected compounds from this patent application (Examples 10, 18, 20, 21, 24, 27, 34, 36, 42, 48, 60, 61, 64, and 68) and the prior art (**D1**, **D3**, **D4**, and **D6**; the pages are detailed in the table). For compounds 18, 27, 34, and 64, the corresponding generic disclosures present in the Markush formula of D1 are detailed.

Present patent application (WO2024163262)	Compounds from prior art
Compound 10 	**D3**, page 182 
Compound 18 	**D1**, page 116  I  wherein R is R^4 is NH_2, R^3 is –Cl, R^9 is H R^1 is –C(O)OR^6 R^6 is C1–C6 alkyl optionally substituted with R^7 R^7 represents one to five substituent groups,

Present patent application (WO2024163262)	Compounds from prior art
	each independently selected from, inter alia, C1–C6 alkyl *The n-decyl group of compound 18 is not individually disclosed in D1 but is encompassed only by combining the generic definitions of R^6 and R^7.*
Compound 20 	**D3**, page 181 
Compound 21 	**D3**, page 183 
Compound 24 	**D3**, page 188  
Compound 27 	**D1**, page 116   wherein R is R^4 is NH_2, R^3 is -Cl, R^9 is H R^1 is H R^2 is -C(O)OR^{6a} R^{6a} is benzyl / (C1–C3 alkylene)-aryl group.

Present patent application (WO2024163262)	Compounds from prior art
Compound 34 	**D1**, page 116   wherein R is R^4 is NH_2, R^3 is -Cl, R^9 is H R^1 is -C(O)OR^6 R^6 is heteroaryl R^2 is -C(O)OR^{6a} R^{6a} is substituted alkylene-aryl groups
Compound 36 	**D6**, page 93 
Compound 42 	**D4**, page 43 
Compound 48 	**D3**, page 184 

Present patent application (WO2024163262)	Compounds from prior art
Compound 60 	**D3**, page 184 
Compound 61 	**D3**, page 185 
Compound 64 	**D1**, page 116   wherein R is R^4 is NH_2, R^3 is -Cl, R^9 is H R^1 is H R^6 is heteroaryl group R^2 is $-C(O)OR^{6a}$ R^{6a} is alkylene-aryl group
Compound 68 	**D3**, page 164 

The repeated disclosure of substantially identical masking groups in unrelated patent families further indicates that these substituents were recognised by the person skilled in the art as a conventional solution for modifying antiviral nucleosides. Their selection therefore reflects ordinary medicinal chemistry practice rather than an inventive contribution over the prior art.

Claims 1-11 are, in substance, a double selection invention with respect to **D1**: (i) compound (A) is itself selected from the genus already disclosed in **D1**, where it is already individualised as compound 4; and (ii) the claimed prodrug-forming substituents (R^1-R^7) are themselves selected from the very same lists of ester, carbonate and carbamate masking groups already enumerated, in essentially the same wording, in the passages of **D1** quoted above. A selection from elements or sub-groups already disclosed, whether individually or as part of a generic teaching, in the prior art can only support an inventive step if it is a *purposive* selection associated with a new and unexpected technical effect, and not an arbitrary subject-matter that was already taught. Such a technical effect must be credibly demonstrated across the claimed scope and must be attributable to the distinguishing features of the claimed subject-matter rather than to properties generally expected from conventional prodrug derivatisation. As demonstrated above, no such unexpected effect has been shown across the breadth of claims 1-11: the available water-solubility data (227/227 compounds) show nothing remarkable, the plasma-stability data are confined to 18/227 compounds, and the single available *in vivo* pharmacokinetic comparison (14/227 compounds) shows only the half-life extension that is the ordinary, expected consequence of the prodrug strategy already taught in **D1**-**D9**. In the absence of any purposive selection, claims 1-11 represent nothing more than an arbitrary selection from the genus already disclosed in D1 and, as such, do not involve inventive step.

Moreover, neither the description nor the experimental section identifies any technical property uniquely associated with the particular combination selected from **D1**. In the absence of evidence demonstrating that the claimed selection possesses characteristics distinguishing it from the remainder of the disclosed genus, the claimed subject-matter represents no more than a routine choice among already contemplated alternatives.

The structural comparison further demonstrates that the claimed substituents are not selected from an unlimited plurality of possibilities, but belong to a comparatively narrow group of conventional prodrug moieties repeatedly employed in closely related antiviral nucleosides. Their recurrence in multiple independent patent families confirms that these substituents formed part of the ordinary medicinal chemistry knowledge available to the person skilled in the art before the priority date.

It is moreover particularly significant that **D2** was filed by the present applicant itself and discloses, for the same compound genus as that disclosed in **D1**, the same generic categories of prodrug-forming modifications (esters, carbonates, carbamates on the 5'- and 3'-hydroxy groups and on the exocyclic amine) now relied upon in the present application. The fact that the applicant's own, earlier-filed patent family already taught this exact prodrug strategy for this exact compound class provides strong evidence that the prodrug approach claimed in the present application formed part of

its own pre-existing, generic research programme, rather than a new inventive insight arising from the specific properties of compound (A). A subsequent application cannot render inventive what the applicant's own prior filing already characterised as a routine, generically-applicable derivatisation technique.

The present application therefore does not disclose a new medicinal chemistry principle, but merely applies the same derivatisation strategy previously presented by the applicant as being generally suitable for this class of antiviral nucleosides. Such routine continuation of an established research direction cannot, by itself, establish an inventive step.

As non-binding background, the UNDP Guidelines for the Examination of Patent Applications Relating to Pharmaceutical Products (2016) reflect a general concern that generic prodrug claims should not be allowed unless the applicant provides evidence that the claimed prodrugs overcome pharmaceutical or pharmacokinetic problems of the parent compound in a non-evident manner. These Guidelines are not relied upon as a source of law before the EPO; they are mentioned only as contextual background consistent with the Article 56 EPC analysis set out above.

In the presence of the compounds disclosed in **D1** and the teachings of **D3-D9** concerning nucleoside prodrugs, no inventive activity can be identified in any of the prodrugs of compound (A) claimed in the present application.

Applying the problem-solution approach, the objective technical problem solved by claims 1-11, on the basis of the closest prior art (**D1**), can be formulated, at most, as the provision of a further prodrug of compound (A) suitable for extended dosing. This is not a novel technical problem: the same problem, in relation to chemically and functionally equivalent NRTTI nucleosides, had already been identified and solved by the same applicant in **D2**, and by third parties in **D3**, **D4**, **D5** and **D6**. The skilled person, faced with this known technical problem and starting from compound (A) of **D1**, would have had reason to apply the very same ester/carbonate/carbamate prodrug toolbox already taught in **D1** and **D2**, as well as and a reasonable expectation of success in applying, given that corresponding prodrug structures had been successfully reduced to practice on directly analogous NRTTI nucleosides in **D3**, **D4**, **D5** and **D6**. There is accordingly no "could-would" gap: the person skilled in the art not only could have arrived at the claimed prodrugs, but would have had reason to do so in the course of routine optimisation.

The claimed subject-matter therefore represents the predictable outcome of applying established prodrug derivatisation techniques to a known antiviral nucleoside in order to obtain the very pharmacokinetic properties that such modifications were already recognised to provide. Since the application fails to demonstrate any unexpected technical effect capable of distinguishing the claimed compounds from those obtainable by the routine application of the prior art, claims 1-11 do not involve an inventive step within the meaning of Article 56 EPC.

Indeed, the prior art consistently teaches that such prodrug modifications are introduced precisely to improve pharmacokinetic behaviour, including prolonged exposure, enhanced stability, improved bioavailability and extended dosing intervals.

The advantages relied upon in the present application therefore correspond to the expected consequences of applying well-established prodrug strategies rather than to any newly discovered technical effect associated with the claimed compounds.

This finding is independently confirmed by **D8** and **D9**, which show that the very same design strategy – replacing a free hydroxy group of a known antiviral nucleos(t)ide analogue with a long-chain ester, carbonate or related acyl masking group for the specific purpose of obtaining a long-acting, slow-release parenteral depot – was being applied, contemporaneously and independently of **D1-D7**, to entirely different drug classes (HIV integrase inhibitors in **D8**; an anti-HBV nucleoside analogue in **D9**). The fact that unrelated research groups, working on unrelated drugs, converged on the same ester-prodrug solution to the same long-acting-dosing problem is itself strong objective evidence that this solution would have been obvious to the person skilled in the art, rather than reflecting inventive ingenuity specific to compound (A) or to the NRTTI field. Claims 1-11 therefore lack an inventive step when the problem-solution approach is applied to the prior art as a whole.

The present application therefore does not disclose a new technical concept, a new prodrug principle, or an unexpected pharmacological property. Instead, it applies established prodrug chemistry to a known antiviral nucleoside using substituents already disclosed, suggested or routinely employed in the prior art for the same technical purpose. Under these circumstances, the claimed subject-matter represents the expected result of ordinary medicinal chemistry practice and cannot involve an inventive step within the meaning of Article 56 EPC.

8.1.2 Pharmaceutical composition – Claims 12–14

Claims 12-14 relate to a pharmaceutical composition comprising an effective amount of any compound of claims 1-11 or a salt thereof and a vehicle (claim 12), the composition being for injection (claim 13), and further comprising additional therapeutic agents (claim 14). These claims do not introduce any independent technical contribution beyond the compounds of claims 1-11. They do not define any specific formulation feature responsible for the alleged long-acting effect, nor do they identify any particular vehicle, excipient, or preparation process that would itself confer an unexpected technical benefit. They merely encompass conventional pharmaceutical compositions comprising the claimed compounds together with routine pharmaceutical carriers or excipients.

The patentability of claims 12-14 therefore depends on that of claims 1-11. Since claims 1-11 do not involve an inventive step, and since no independent formulation-related technical contribution has been identified or demonstrated, claims 12-14 likewise lack an inventive step under Article 56 EPC.

As mentioned previously, the compounds derived from claims 1-11 lack inventive step with respect to **D1-D9**. With respect to pharmaceutical compositions comprising such compounds, **D1**, **D3**, and **D6** specifically disclose pharmaceutical compositions, as shown below:

"20. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
21. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier and further comprising an effective amount of an anti-HIV agent selected from an anti-HIV antiviral agent, an immunomodulator, or anti-infective agent." (**D1**, claims 20 and 21, page 122, highlights ours)

"23. A pharmaceutical composition comprising a compound according to any of Claims 1-22, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
(...)
26. The composition of Claim 23, wherein the composition is formulated as a long acting parenteral injection." (**D3**, claims 23 and 26, page 191, highlights ours)

"30. A pharmaceutical composition comprising an adenosine derivative of any one of claims 1-29 and a pharmaceutically acceptable carrier.
(...)
34. The pharmaceutical composition of claim 32 or 33, wherein the pharmaceutical composition is suitable for intramuscular or subcutaneous injection." (**D6**, claims 30 and 34, page 161, highlights ours)

Therefore, considering that the compounds of claims 1-11 lack inventive step with respect to the teachings of **D1-D9**, and since **D1**, **D3**, and **D6** disclose pharmaceutical compositions, the person skilled in the art would have had reason to formulate pharmaceutical compositions comprising the claimed compounds and, where appropriate, to combine them with other anti-HIV agents, with a reasonable expectation of obtaining an active composition for the treatment of HIV infection. Therefore, claims 12-14 lack inventive step.

The injectable character of claim 13 adds nothing inventive either. **D8** independently confirms that formulating a lipophilic ester prodrug of a known anti-HIV agent as an injectable nanocrystal/nanoparticle suspension, specifically to obtain a long-acting intramuscular depot, was a routine formulation choice in this technical field, applied to an unrelated drug class with the same objective and equivalent expected result.

Accordingly, claims 12-14 merely relate to routine pharmaceutical compositions which, in themselves, do not involve an inventive step. Since no additional formulation-related technical contribution has been identified or demonstrated, claims 12-14 likewise fail to satisfy the requirements of Article 56 EPC.

8.1.3 Method of treatment – Claims 15–20

Claims 15-20 relate to a method for the treatment or prophylaxis of HIV infection (claim 15), or for delaying the onset or progression of AIDS in a subject (claim 16),

comprising administering an effective amount of any of the compounds of claims 1-11, their salts, or pharmaceutical composition comprising such compounds (claim 16), optionally in combination with additional therapeutic agents (claims 17-18), at a dosing interval of approximately once a month to approximately once every twelve months (claims 19-20).

The claimed therapeutic methods do not define a new medical indication, a new biological target or a new mechanism of action. Rather, they relate to the administration of the claimed compounds for the same therapeutic purpose already disclosed in the prior art, namely the treatment or prophylaxis of HIV infection through inhibition of HIV reverse transcriptase.

Since the compounds derived from claims 1-11 lack inventive step with respect to **D1-D9**, and since **D1**, **D3**, and **D6** specifically disclose treatment methods, as shown below, claims 15-20 lack inventive step.

> "23. A method for the treatment or prophylaxis of infection by HIV or for the treatment, prophylaxis, or delay in the onset of AIDS in a subject in need thereof, which comprises administering to the subject an effective amount of the compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof." (**D1**, claim 23, page 123, highlights ours)

> "27. A method of treating an HIV infection in a patient comprising administering to the subject a compound of any of Claims 1-22, or a pharmaceutically acceptable salt thereof.
> 28. A method of preventing an HIV infection in a patient at risk for developing an HIV infection, comprising administering to the subject a compound of any of Claims 1-22, or a pharmaceutically acceptable salt thereof." (**D3**, claims 27 and 28, page 191, highlights ours)

> "43. A method for treating an HIV infection, comprising administering a subject in need thereof an effective dosage of the pharmaceutical composition of any one of claims 30-42.
> 44. A method for preventing an HIV infection, comprising: administering a subject in need thereof an effective dosage of the pharmaceutical composition of any one of claims 30-42.
> (...)
> 57. The method of any one of claims 43-56, further comprising an effective dosage of one or more additional antiviral agent selected from lenacapavir, atazanavir, atazanavir sulfate, bictegravir, cabotegravir, darunavir, dolutegravir, doravirine, efavirenz, tenofovir disoproxil fumarate, tenofovir alafenamide, etravirine, a combination of darunavir and cobicistat, rilpivirine, MK-8507 or a combination thereof." (**D6**, claims 43, 44 and 57, pages 163-164, highlights ours)

Considering that the compounds of claims 1-11 lack inventive step with respect to the teachings of **D1-D9**, and since **D1**, **D3**, and **D6** specifically disclose treatment methods, the person skilled in the art would have had reason to apply the known methods of treatment or prophylaxis of HIV infection that include these compounds. Therefore, claims 15-20 lack inventive step.

The specific dosing intervals recited in claims 19-20 (approximately once a month to approximately once every twelve months, including once every three or six months) likewise fail to add any inventive contribution. **D8** expressly teaches that the same class of chemical modification (replacement of a free hydroxyl with a long-chain ester) applied to a different anti-HIV drug class achieves sustained therapeutic drug levels for six months or longer after a single intramuscular dose, and that dosing intervals of "once every 1 to 12 months or even less frequently" are the expected and intended consequence of this type of prodrug modification. The dosing intervals of claims 19-20 are therefore simply the predictable result of applying a known prodrug strategy, already known to produce such a pharmacokinetic outcome, and cannot support an inventive step.

8.1.4 Compound for use – Claims 21–22

Claims 21-22 relate to a compound of any one of claims 1-11 for use in the preparation of a medicament for the inhibition of HIV reverse transcriptase for the treatment or prophylaxis of HIV infection (claim 21), or for use in therapy (claim 22).

Since the compounds of claims 1-11 lack inventive step for the reasons set out above, claims 21-22 cannot derive an inventive step merely by being drafted in a medical-use format. D1 discloses, in its general description, the same HIV/AIDS therapeutic indication, and D3 (claims 29 and 30, pages 191-192) independently discloses compounds for use in treating or preventing HIV infection.

The therapeutic indication relied upon in claim 21 — treatment or prophylaxis of HIV infection/AIDS — is already disclosed in D1 and D3, while the alleged HIV reverse transcriptase inhibition follows from the same known class of nucleoside reverse transcriptase inhibitors discussed above. Claim 22 is broader still, since it merely refers to use in therapy without defining any specific therapeutic use capable of conferring a further inventive contribution. Accordingly, claims 21-22 lack inventive step under Article 56 EPC.

8.2 Exclusion from patentability under Article 53(c) EPC – Claims 15–20

Claims 15-20 relate to a method of treatment or prophylaxis of HIV infection (claim 15), or delaying the onset or progression of AIDS in a subject (claim 16), comprising administering an effective amount of any of the compounds of claims 1-11, their salts or pharmaceutical composition comprising such compounds (claim 16), together with additional therapeutic agents (claims 17-18), at a dosing interval of approximately once a month to approximately once every twelve months (claims 19-20).

Claims 15-20 are excluded from patentability for the following reason:
Article 53(c) EPC excludes from patentability "methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods." As claims 15-20 are drafted as methods comprising the step of administering the claimed compound, salt or composition to a subject, they fall squarely within this exclusion and should not be granted in their present method-claim format, irrespective of whether the underlying compounds and compositions are otherwise patentable.

The presence of specific dosing-interval features in claims 19-20 does not remedy this defect. In *G 2/08* (Dosage regime/ABBOTT RESPIRATORY) the Enlarged Board of Appeal confirmed that a novel and inventive dosing regimen can confer patentability on a known substance only when claimed in the purpose-limited "compound/composition for use" format of Article 54(5) EPC, and that the former "Swiss-type" claim format is no longer admissible. Claims 19-20, however, are drafted as a direct method of treatment rather than in the Article 54(5) EPC format. The dosage-regimen feature is therefore not capable of bringing claims 19-20 outside the Article 53(c) EPC exclusion applicable to claims 15-18.

For completeness, claims 21–22 are drafted as product-for-use claims rather than as direct methods of treatment involving an act of administration to a subject. Accordingly, no objection under Article 53(c) EPC arises in respect of claims 21–22.

8.3 Lack of clarity and sufficiency of disclosure – Claims 1–22

Article 84 EPC requires that the claims be clear and concise and be supported by the description. Article 83 EPC requires that the European patent application disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, across the whole scope of the claims. As set out below, claims 1-22 fail to meet these requirements.

8.3.1 Claims 1–11

Claims 1-11 of this application relate to Markush formulas I, II, III, IV, V, and VI (claims 1-9); 227 selected compounds derived from the Markush formulas (claim 10); 14 selected compounds (claim 11); or a pharmaceutically acceptable salt thereof. These claims seek to protect a large number of compounds and their pharmaceutically acceptable salts; however, the description provides details of the synthesis of only 73 compounds (Examples 1-73, pages 59-114 of the description). For the remaining selected compounds (74 to 227), no details of the chemical synthesis used to obtain these compounds are provided; it is simply mentioned that procedures similar to those detailed in Examples 1-73 were used, for example:

"[0313] The Examples in the table below were prepared using procedures similar to those described in Example 12, from the appropriate starting material." (page 116, description of the present patent application)

Furthermore, while water solubility tests (pages 160-162, description) and *in vitro* potency tests (pages 162-165) were performed for all 227 selected compounds, *in vitro* plasma stability tests (page 165) were performed for only 18 of the 227 compounds. Finally, *in vitro* metabolic stability tests (page 166) and the single *in vivo* plasma exposure test, in rats, were performed for only 14 of the 227 compounds (page 167 and Figures 1-15, comparison of compound A vs. 14 prodrugs of compound A).

Therefore, claims 1-11 are not adequately supported by the description of the application and do not meet the sufficiency-of-disclosure requirement.

Claims 1-11 are, in addition, objectionable under Article 84 EPC for lack of clarity in their own right, independently of the support issue discussed above. Formula (VI) defines X, Y, Z and W each as independently selectable from several distinct linking groups, including, in each case, "a bond", while R^1-R^3 are independently selectable down to hydrogen. The claim does not exclude combinations in which a divalent linking group (e.g., X = $–CR^5R^6$-O-C(=O)-O-) is combined with R^2 = hydrogen, nor combinations in which W and Z are simultaneously a bond while R^7 and R^1 are simultaneously hydrogen, i.e. combinations that either fail to define a chemically meaningful substituent or collapse back onto compound (A) itself (which the claim already excludes by the proviso that "at least one of R^1, R^2 and R^3 is not hydrogen", a proviso which itself confirms that the formula as drafted otherwise reads on compound (A)). The person skilled in the art is left without clear guidance as to which of the very large number of permutations defined by Formula (VI) are chemically operable and intended to be covered, contrary to Article 84 EPC.

Claims 1 and 2 raise a further, independent clarity objection under Article 84 EPC. Although drafted as separate independent claims directed, respectively, to compounds of Formula (VI) and Formula (I), the substituent definitions of claim 2 fall entirely within the broader definitions of claim 1 once the optional group –W-R^7 of claim 1 is set equal to hydrogen. Claims 1 and 2 accordingly relate, in substance, to the same subject-matter and differ only in the manner in which that subject-matter is defined, contrary to the requirement of Article 84 EPC, second sentence, that the claims be concise.

Claim 10, which lists 227 selected compounds, is itself unclear: compound 28 is listed twice, and compounds 75 and 76 are identical, both claim 10 itself and in the corresponding list of compounds given elsewhere in the description. The person skilled in the art is accordingly left in doubt as to the actual number and identity of the compounds intended to be covered by claim 10, contrary to Article 84 EPC.

A further inconsistency arises between the claims and the description. Paragraph [0086] of the description discloses a phosphate ester prodrug modification (-O-P(=O)(OH_2)) as a contemplated embodiment of the invention, yet this particular modification does not fall within the scope of any of claims 1-11 as presently drafted. This discrepancy between what is described as part of the invention and what is

actually claimed leaves the person skilled in the art in doubt as to the true matter for which protection is sought, contrary to Article 84 EPC.

This amounts to a failure to meet the requirements of Article 83 EPC (insufficiency of disclosure across the claimed scope) and, since the unsupported breadth of claims 1-11 is not commensurate with the technical contribution actually demonstrated, also of Article 84 EPC (lack of support by the description).

8.3.2 Claims 12–14

Claims 12-14 relate to pharmaceutical compositions comprising the compounds of claims 1-11, including injectable compositions and compositions further comprising additional therapeutic agents. However, the claims do not define any formulation feature that is linked to the alleged long-acting effect, nor does the description demonstrate that any particular formulation provides an additional technical contribution over the compounds themselves.

Accordingly, to the extent that the application relies on a long-acting formulation effect, claims 12-14 are not supported over their full breadth by the description, contrary to Article 84 EPC. In addition, the application does not enable the person skilled in the art to achieve such an effect across the full scope of the claimed compositions, contrary to Article 83 EPC.

8.3.3 Claims 15–20

Claims 15-20 relate to a method of treatment or prophylaxis of HIV infection (claim 15), or delaying the onset or progression of AIDS in a subject (claim 16), comprising administering an effective amount of any of the compounds of claims 1-11, their salts, or pharmaceutical composition comprising such compounds (claim 16), with additional therapeutic agents (claims 17-18), at a dosing interval of approximately once a month to approximately once every twelve months (claims 19-20). These claims are written generically, do not specify doses, salts, their amounts or proportions, and the dosing intervals are approximate, the word “approximately” in claims 19-20 being used without any defined tolerance or measurable boundary, so that the person skilled in the art cannot determine with certainty whether a given dosing interval falls inside or outside the claimed range. Therefore, claims 15-20 lack clarity. Furthermore, the objection under Article 83 EPC is not based merely on the absence of clinical trials. Rather, the application does not make it credible that the alleged long-acting effect is achieved across the full breadth of claims 15-20. In particular, the limited in vitro data and the single in vivo rat study (pages 166-167 and Figures 1-15) do not provide sufficient support for dosing intervals ranging from approximately once monthly to approximately once every twelve months, nor for the broadly claimed therapeutic regimens and combinations with additional anti-HIV agents. In this respect, claims 15-20 do not meet the sufficiency-of-disclosure requirement under Article 83 EPC.

Claims 15-20 accordingly fail to meet the requirements of Article 84 EPC and Article 83 EPC, in addition to being excluded from patentability under Article 53(c) EPC as set out in Section 8.2. above.

8.3.4 Claims 21–22

Claims 21–22 relate to compounds or salts of any one of claims 1–11, or pharmaceutical compositions according to any one of claims 12–14, for medical use. Claim 21 refers to such compounds, salts or compositions for use in the preparation of a medicament for the inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of HIV infection, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS. Claim 22 refers more broadly to such compounds, salts or compositions for use in therapy.

Claim 21 combines elements of two distinct forms of medical-use claim wording. It uses purpose-limited product language while also referring to "the preparation of a medicament", which corresponds to the terminology formerly used in Swiss-type claims. As drafted, the claim therefore does not unambiguously define whether the claimed subject-matter is directed to a purpose-limited product for use under Article 54(5) EPC or incorporates the former medicament-manufacture claim format. Claim 21 therefore fails to clearly define the category and scope of protection sought and fails to comply with Article 84 EPC.

Furthermore, the available experimental evidence, consisting of limited in vitro studies and a single in vivo rat study relating to only a small subset of the claimed compounds, does not make it credible that the alleged therapeutic effects are achieved across substantially the whole breadth of claims 21–22. In relation to claim 21, the available data also do not make the alleged extended-dosing effect credible across substantially the whole scope claimed. This concern is particularly relevant to claim 22, which refers broadly to use in therapy without defining a particular therapeutic indication.

Accordingly, claim 21 fails to meet the requirements of Article 84 EPC. Claims 21–22 also fail to meet the requirements of Article 83 EPC to the extent that the alleged therapeutic effects are not made credible across substantially the whole scope of the claims and, in the case of claim 21, the alleged extended-dosing effect is likewise not made credible across substantially the whole scope of the claim..

8.4 Lack of unity of invention – Claims 1–22

An objection of lack of unity arises a posteriori once the common concept relied upon in the application is assessed in the light of the prior art. Article 82 EPC requires that a European patent application relate to one invention only or to a group of inventions so linked as to form a single general inventive concept.

Under Rule 44(1) EPC and the corresponding EPO Guidelines, Part F-V, 3, unity between a group of claimed inventions exists only where there is a technical relationship involving one or more of the same or corresponding "special technical

features", namely those technical features that define the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The principal feature common to claims 1–22 is that they concern prodrugs of 4-amino-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl-2'-deoxynucleoside, referred to in the application as compound (A), and their use in the treatment or prophylaxis of HIV infection. However, compound (A), its inhibition of HIV reverse transcriptase and its therapeutic use against HIV are already disclosed in **D1. D1** also expressly contemplates the preparation of prodrugs of compound (A).

As explained in Section 8.1 above, the individual families of prodrug-forming modifications now claimed, including ester, carbonate, carbamate, amino-group and phosphate-related modifications, were independently known or suggested in D1–D9. Furthermore, the application does not credibly demonstrate a common unexpected technical effect achieved across substantially the entire breadth of these structurally distinct prodrug families.

Once the known parent compound, its known therapeutic activity and the generally known concept of converting it into a prodrug are disregarded, no common technical feature remains that can be regarded as making a contribution over the prior art within the meaning of Rule 44(1) EPC.

The claimed subject matter therefore appears to comprise several technically distinct groups of prodrug modifications, including at least:

(i) ester derivatives at the 3' and/or 5' hydroxy groups;

(ii) carbonate and carbamate derivatives;

(iii) derivatives formed by modification of the exocyclic amino group;

(iv) phosphate, phosphoramidate or related nucleotide-prodrug derivatives; and

(v) combinations of two or more of those modification types.

These groups are structurally different, are supported by different teachings in the prior art and are not linked by a common, credibly demonstrated unexpected technical effect. Accordingly, if the common concept based on compound (A) and its conversion into a prodrug is found not to constitute a special technical feature over D1, the claims lack unity a posteriori within the meaning of Article 82 and Rule 44(1) EPC.

The precise grouping of the remaining inventions may ultimately depend on whether any narrower subject matter is found to involve an inventive step. Nevertheless, in their present breadth, claims 1–22 do not appear to be linked by a single general inventive concept.

Yours faithfully,
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on behalf of:

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Public Association “Positive Initiative” (Asociația Obștească “Inițiativa Pozitivă”)
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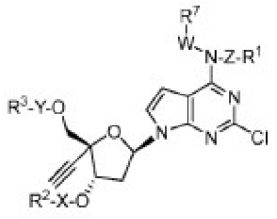
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Annex – Claims

1. A compound of Formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

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;

Y is selected from -C(=O)-, -C(=O)-O-, -CR^5R^6-O-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;

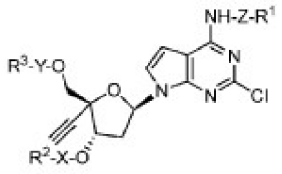
R^3 is selected from the group consisting of hydrogen, C_{1-21} alkyl, $(CR^5R^6)_z$-C_{3-12} cycloalkyl, $(CR^5R^6)_z$-C_{5-12} heterocyclyl, $(CR^5R^6)_z$-C_{6-12} aryl, and $(CR^5R^6)_z$-C_{5-12} heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, or heteroaryl group can be optionally substituted 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.

2. A compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

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;

Y is selected from -C(=O)-, -C(=O)-O-, -CR^5R^6-O-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)- 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, and $(CR^5R^6)_z$-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, and $(CR^5R^6)_z$-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;

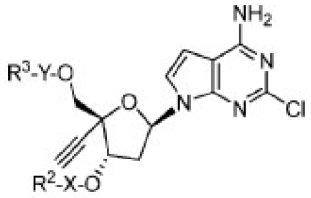
R^3 is selected from the group consisting of hydrogen, C_{1-21} alkyl, $(CR^5R^6)_z$-C_{3-12} cycloalkyl, $(CR^5R^6)_z$-C_{5-12} heterocyclyl, $(CR^5R^6)_z$-C_{6-12} aryl, and $(CR^5R^6)_z$-C_{5-12} heteroaryl, wherein said alkyl, cycloalkyl, heterocyclyl, aryl or heteroaryl group can be optionally substituted with one to three groups independently selected from halo, C_{1-6} alkyl, C_{3-12} cycloalkyl and hydroxy;

R^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

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.

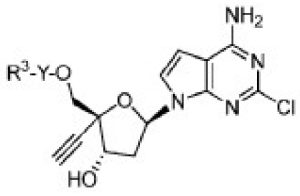
3. The compound of claim 1 or 2, wherein the compound is of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

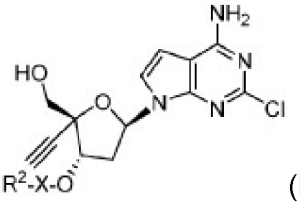
4. The compound of claim 1 or 2, wherein the compound is of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1 or 2, wherein the compound is of Formula (IV):



(IV)

or a pharmaceutically acceptable salt thereof.

6. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein

X is selected from -C(=O)-, -CR^5R^6-O-C(=O)-, and a bond;

Y is selected from -C(=O)-, -CR^5R^6-O-C(=O)-, and a bond;

Z is a bond, and R^1 is hydrogen;

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, and $(CR^5R^6)_z$-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; and

R^3 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, and $(CR^5R^6)_z$-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,

wherein z is 0, 1, 2, 3, 4, 5, or 6.

7. The compound of any one of claims 1-5, or a pharmaceutically acceptable salt thereof, wherein

X is selected from -C(=O)-O-, -CR^5R^6-O-C(=O)-O-, and a bond;

Y is selected from -C(=O)-O-, -CR^5R^6-O-C(=O)-O-, and a bond;

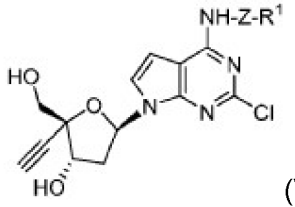
Z is a bond, and R^1 is hydrogen;

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, and $(CR^5R^6)_z$-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; and

R^3 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, and $(CR^5R^6)_z$-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,

wherein z is 0, 1, 2, 3, 4, 5, or 6.

8. The compound of claim 1 or 2, wherein the compound is of Formula (V):



(V)

or a pharmaceutically acceptable salt thereof.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein:

X is selected from -C(=O)-, -C(=O)-O-, and a bond;

Y is selected from -C(=O)-, -C(=O)-O-, and a bond;

Z is a bond, and R^1 is hydrogen;

R^1 is selected from hydrogen and C_{1-14} alkyl;

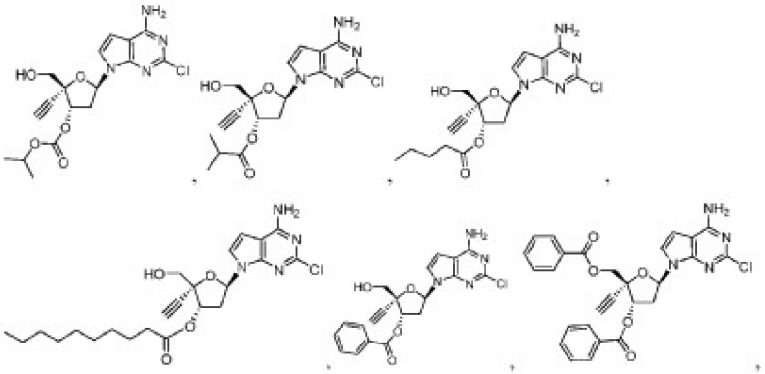
R^2 is selected from C_{1-10} alkyl, $(CR^5R^6)_z$-C_{3-12} cycloalkyl, and $(CR^5R^6)_z$-C_6 aryl, wherein said aryl can be optionally substituted with a halo; and

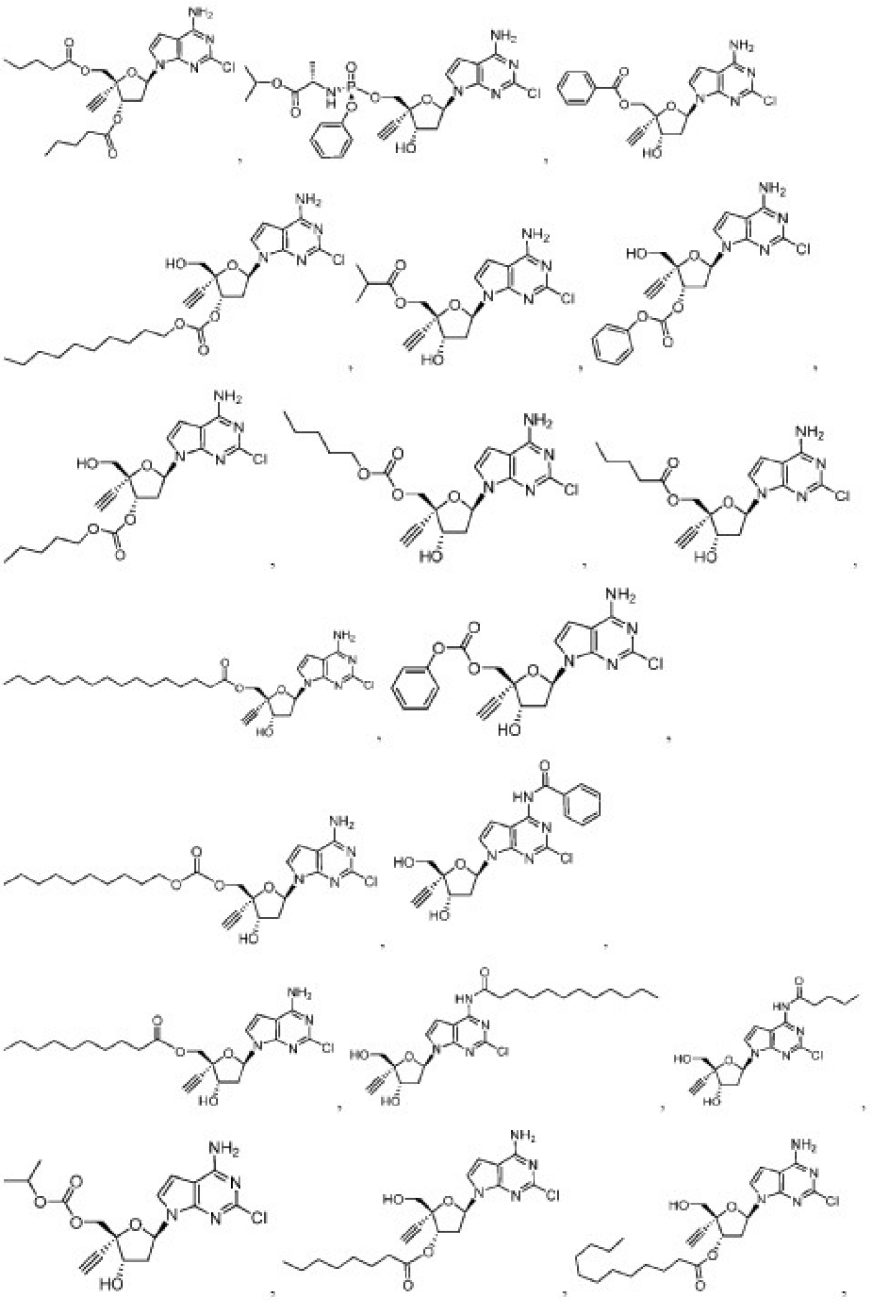
R^3 is selected from C_{1-10} alkyl, $(CR^5R^6)_z$-C_{3-12} cycloalkyl, and $(CR^5R^6)_z$-C_6 aryl, wherein said aryl can be optionally substituted with a halo, and

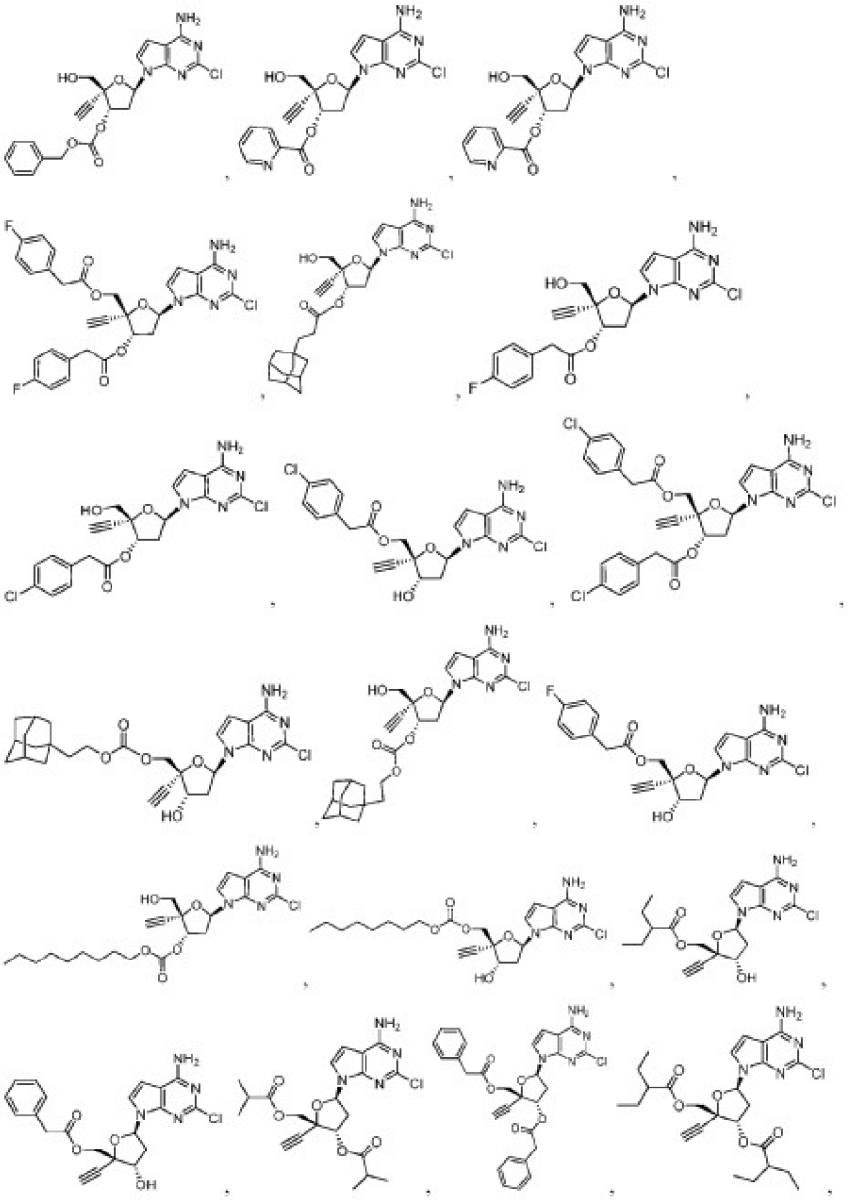
wherein R^5 and R^6 are hydrogen,

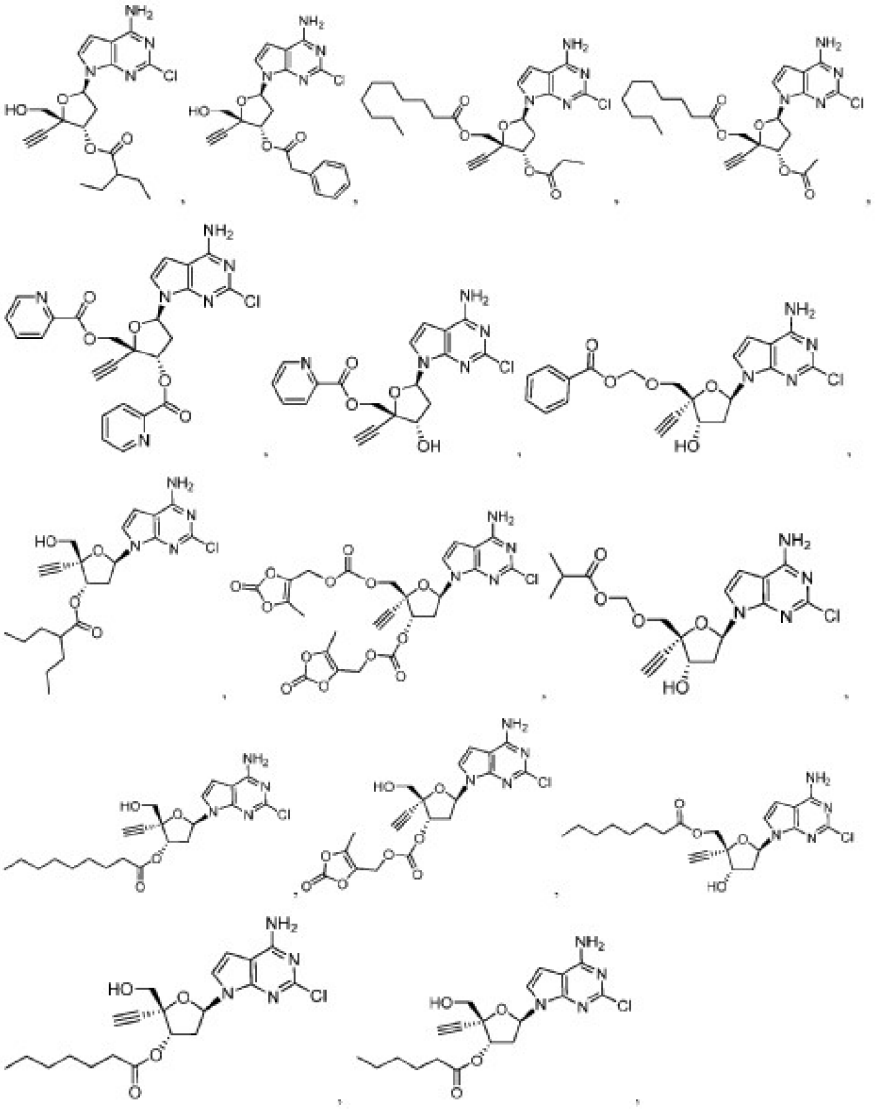
wherein z is 0, 1, 2, 3, 4, 5, or 6.

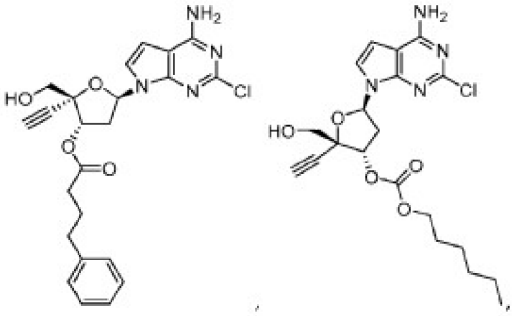
10. The compound of any one of claims 1-9 having the structure:

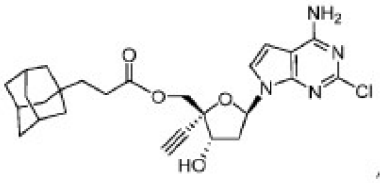


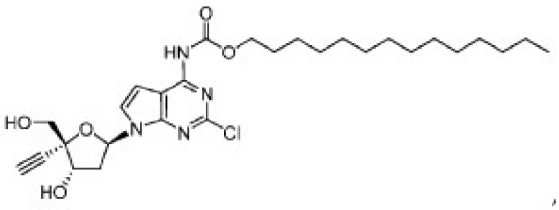


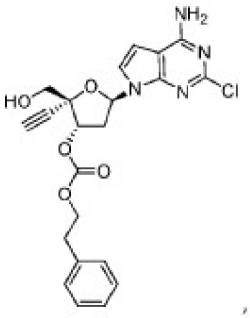


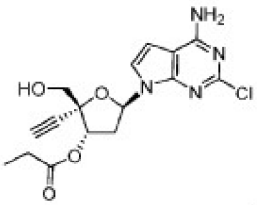


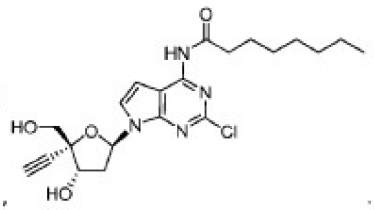


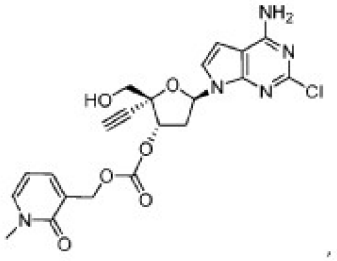


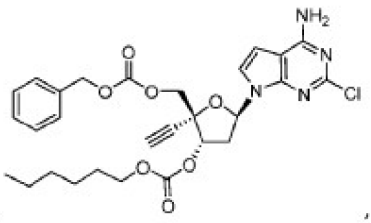


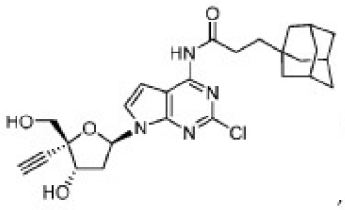


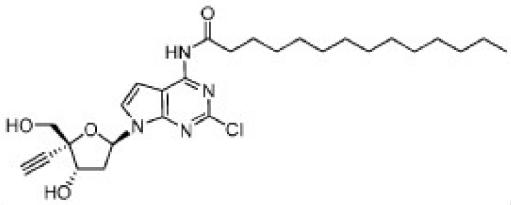


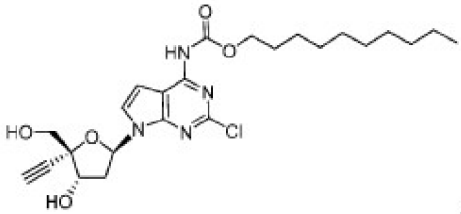


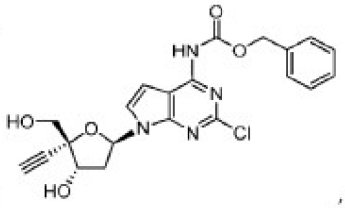


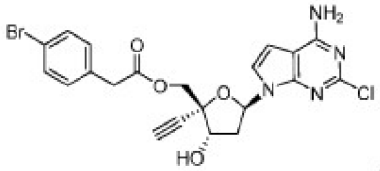


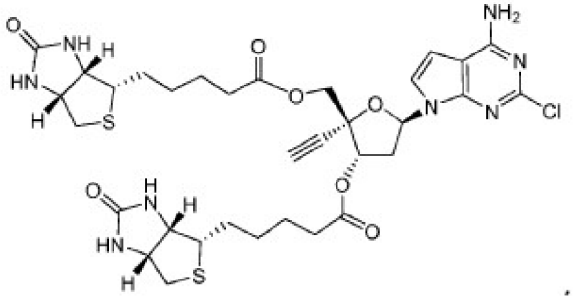


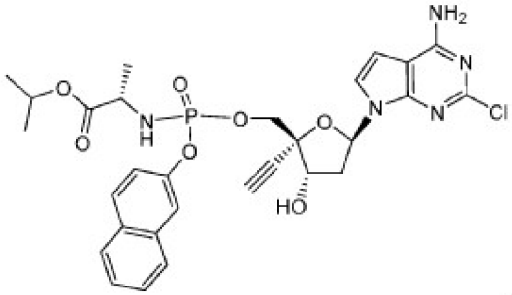


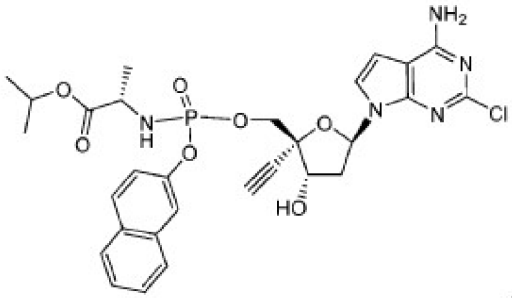


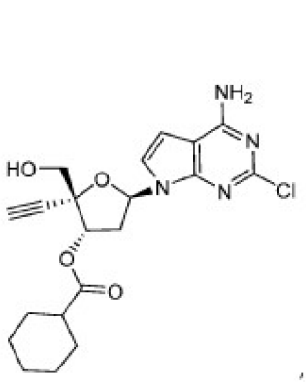


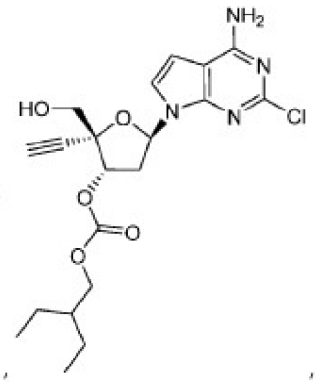


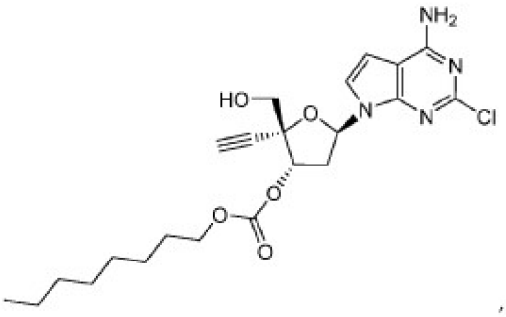


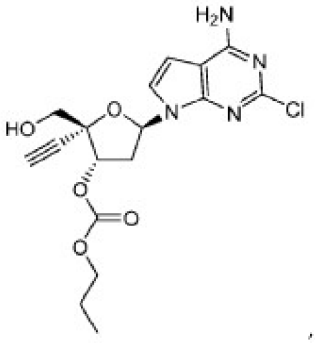


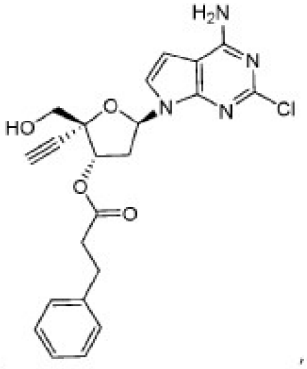


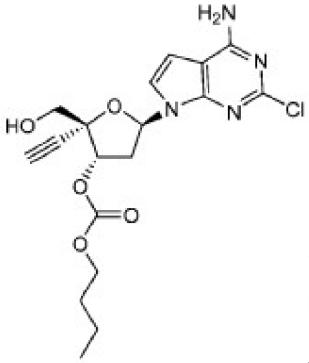


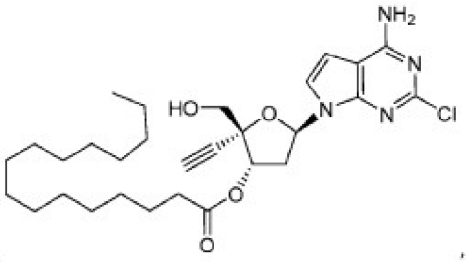


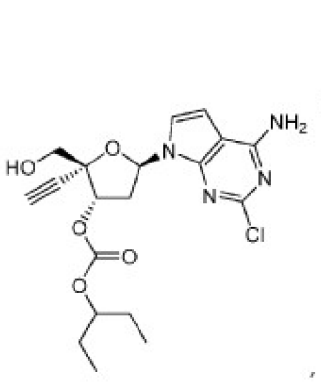


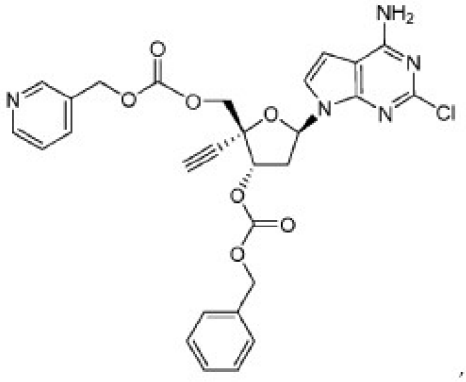


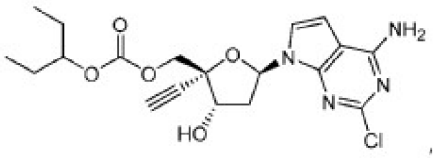


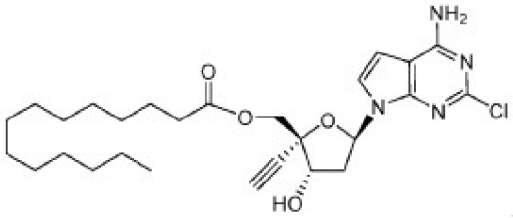


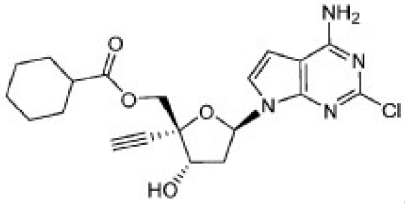


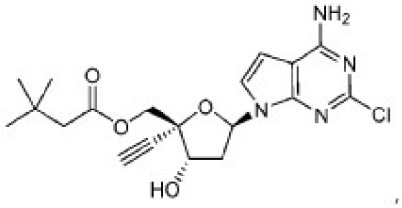


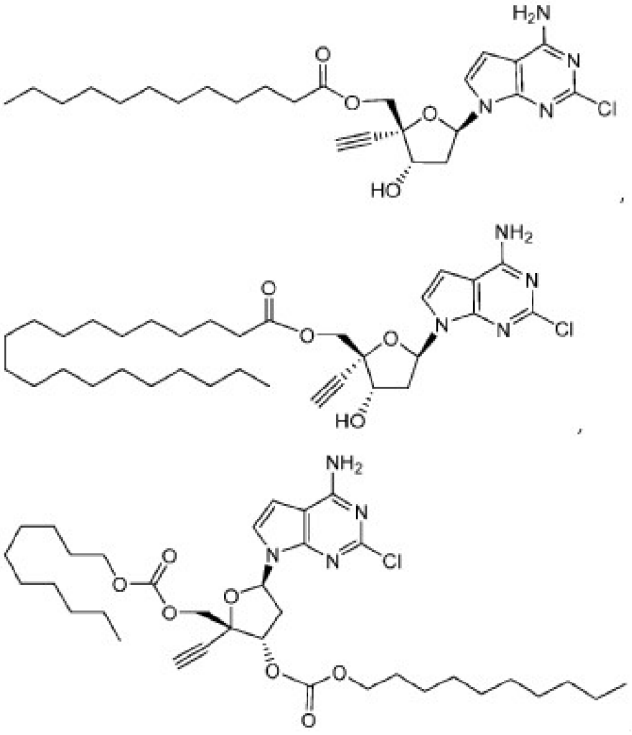


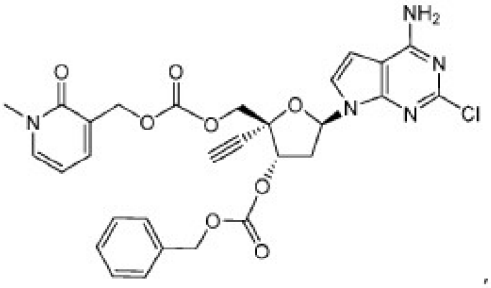


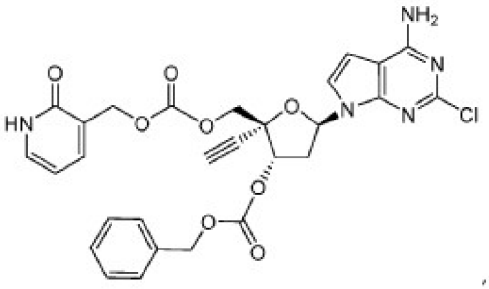


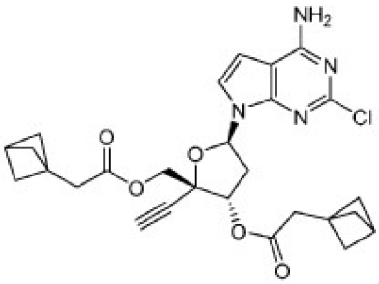


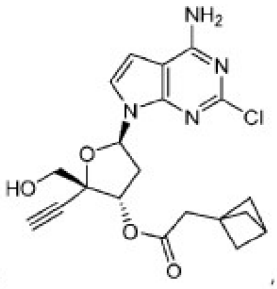


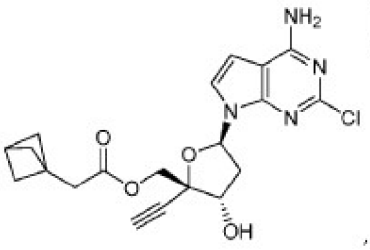


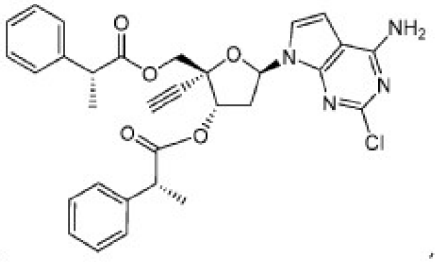


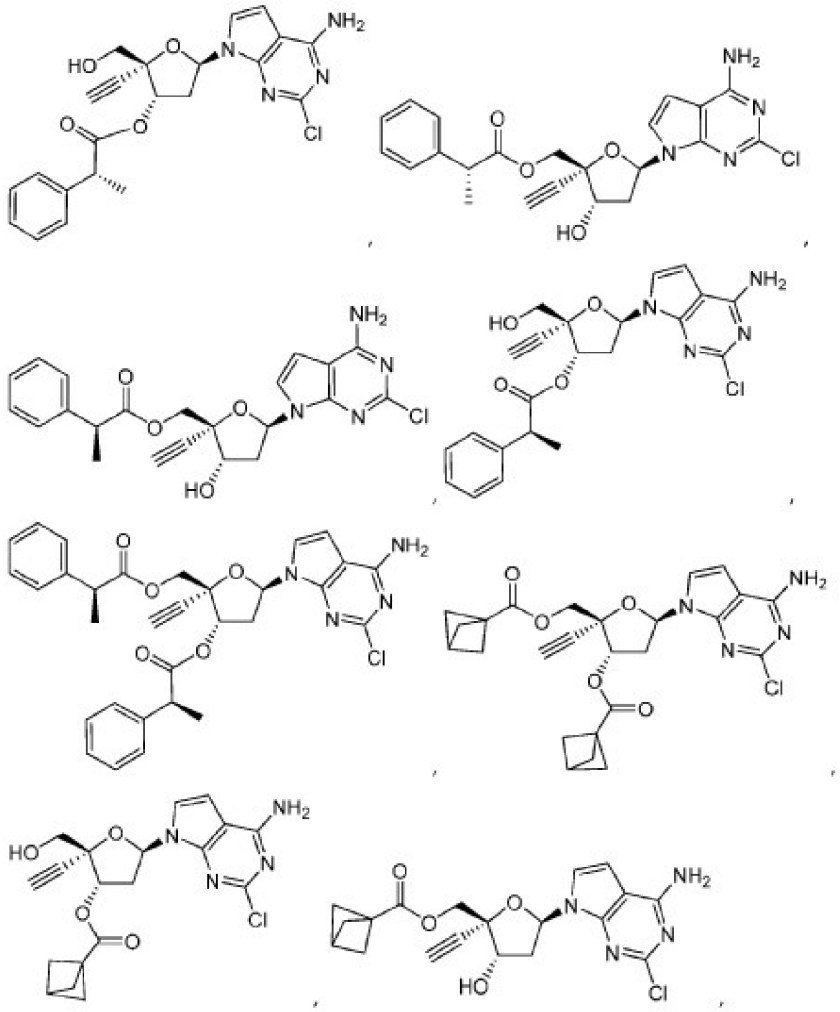


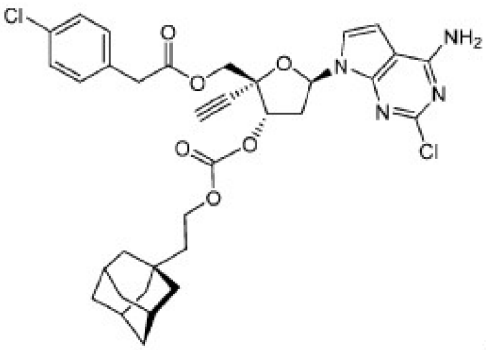


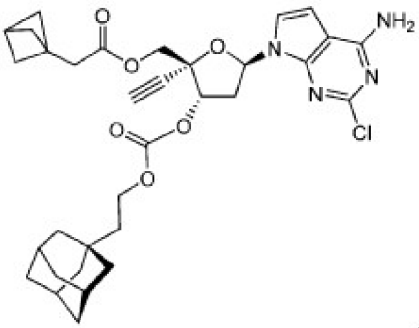


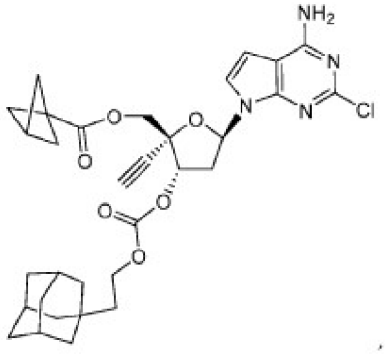


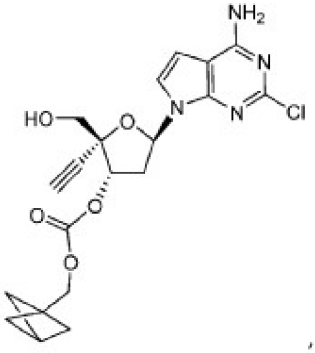


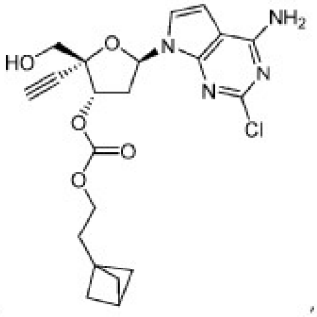


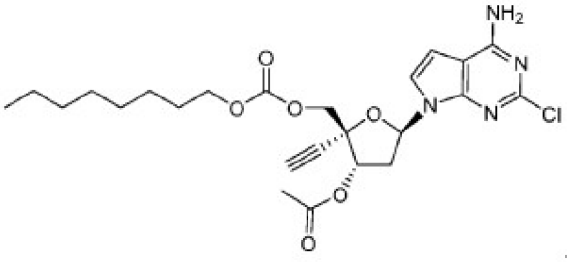


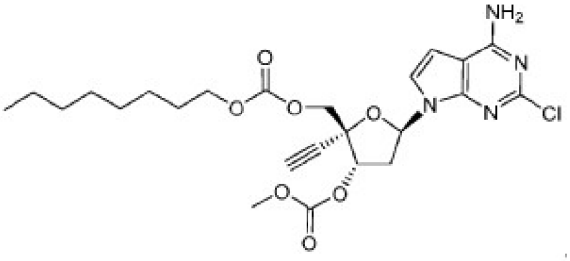


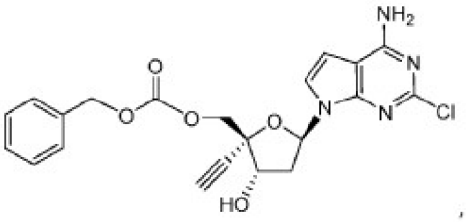


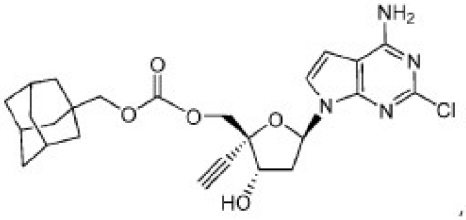


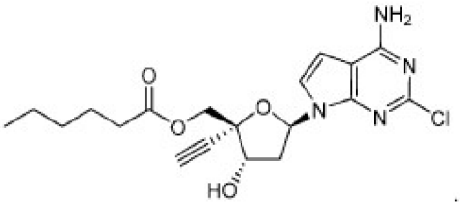


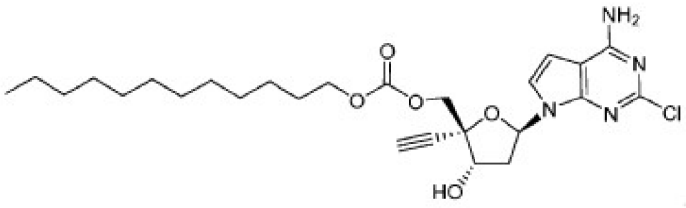


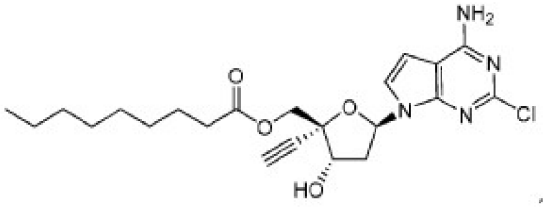


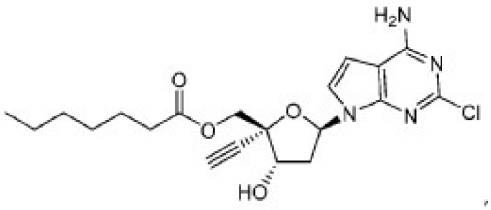


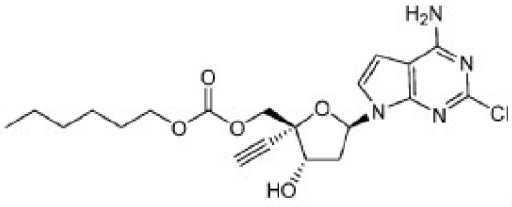


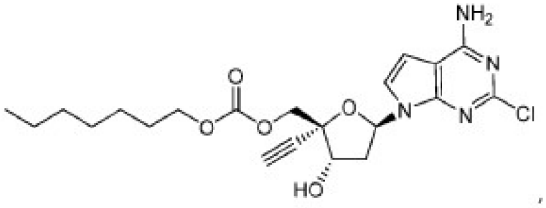


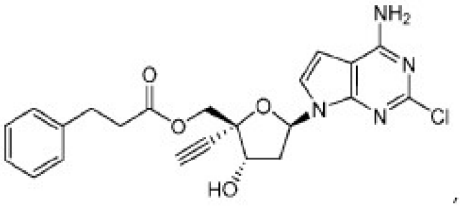


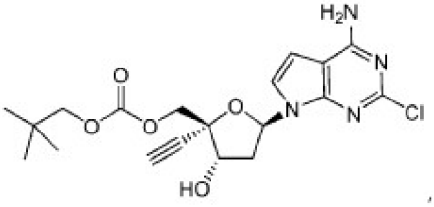


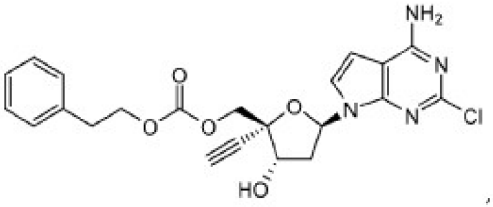


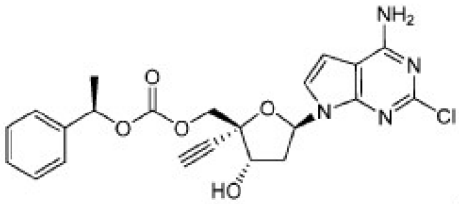


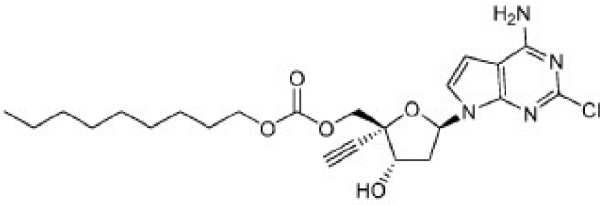


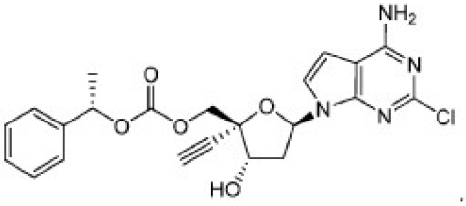


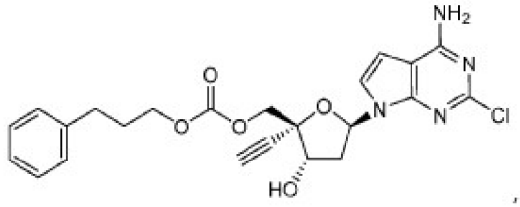


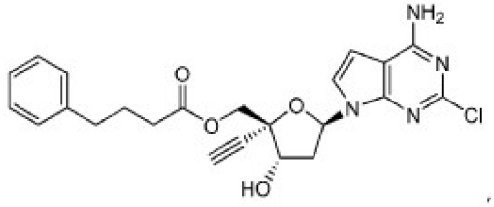


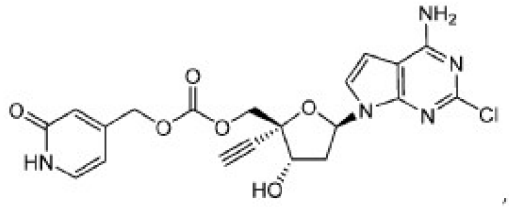


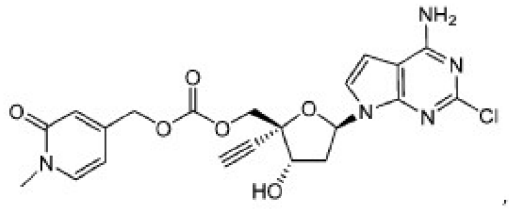


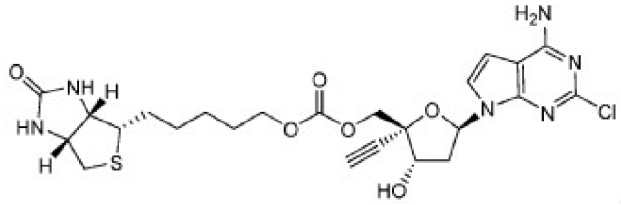


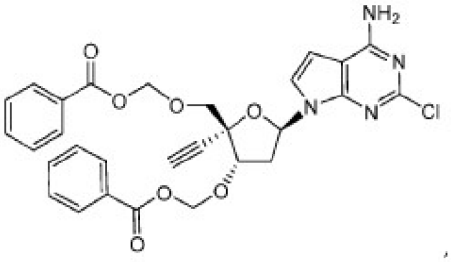


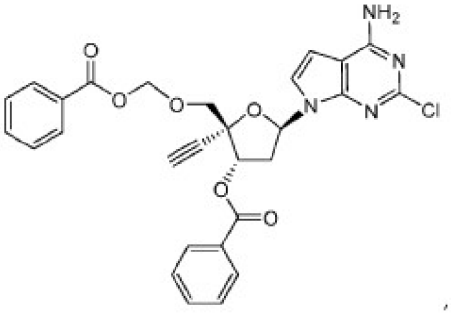


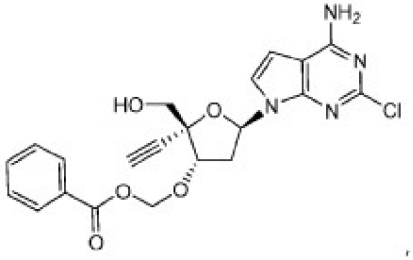


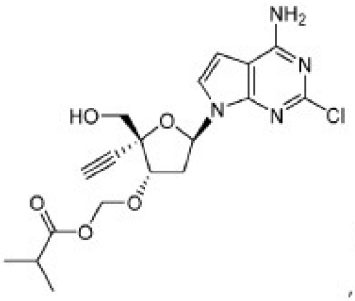


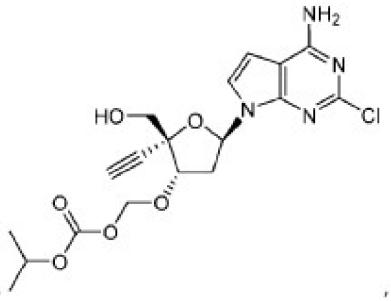


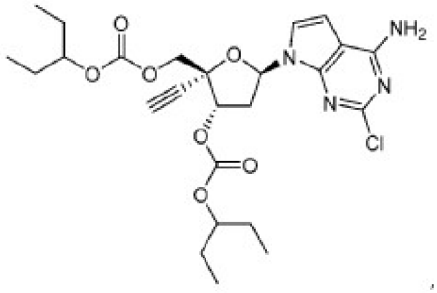


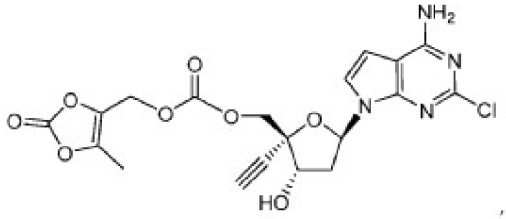


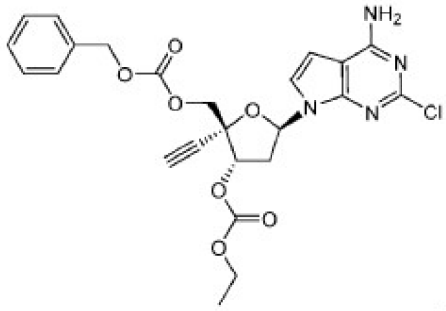


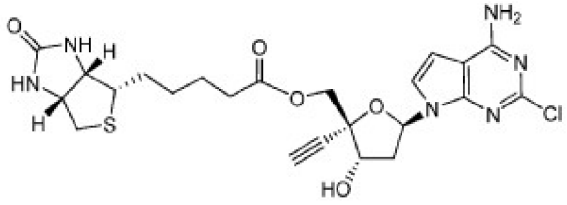


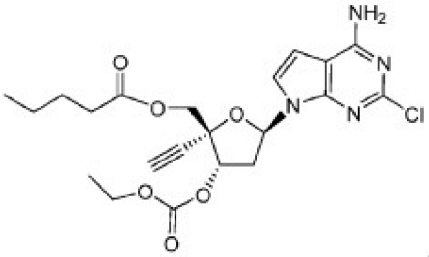


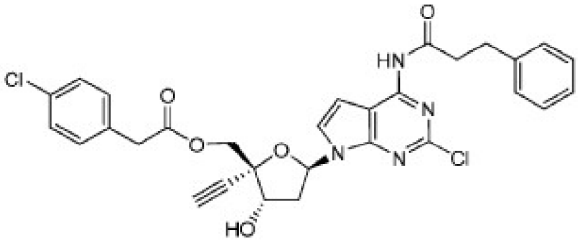


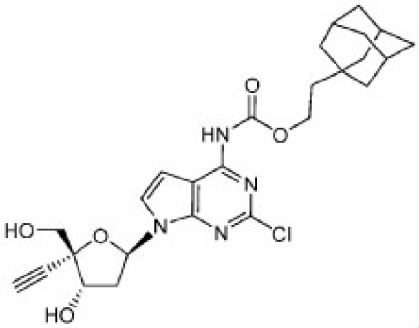


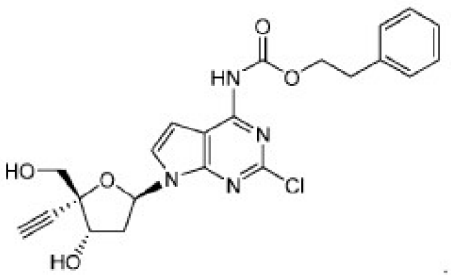


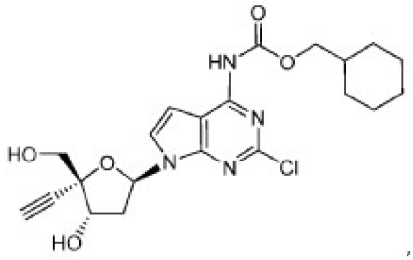


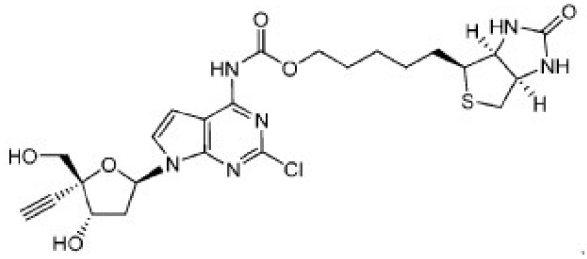


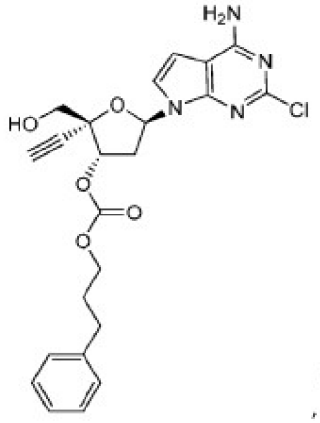


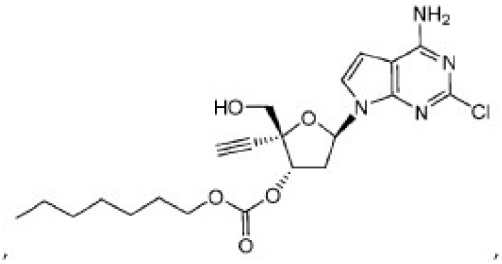


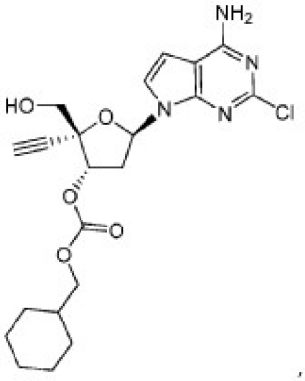


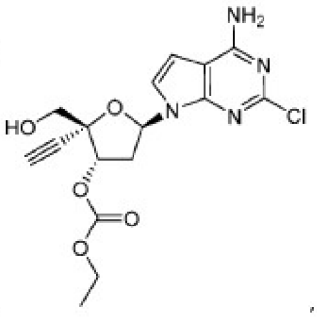


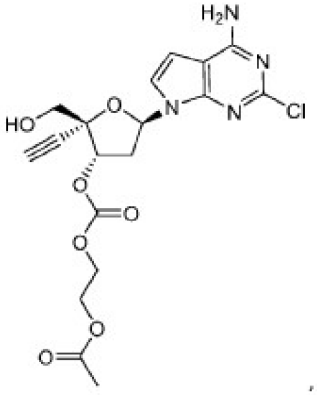


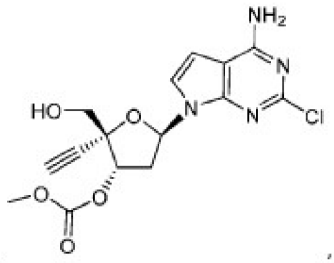


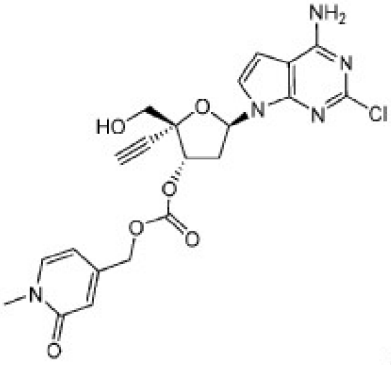


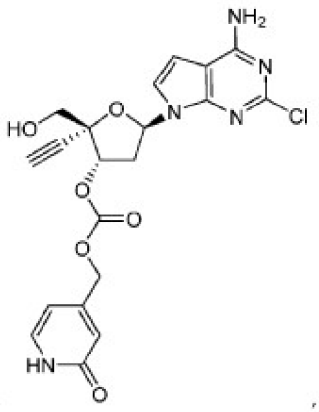


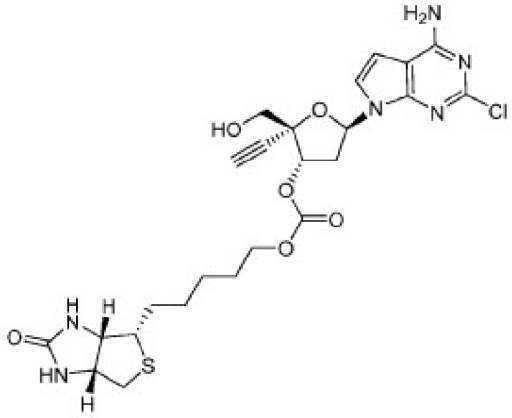


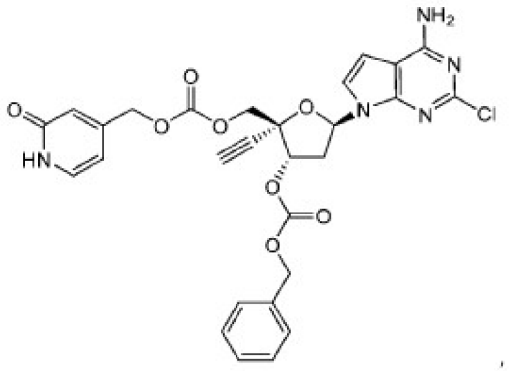


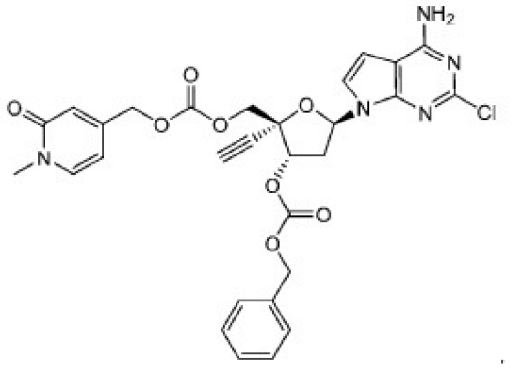


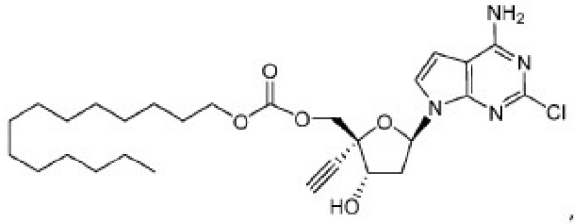


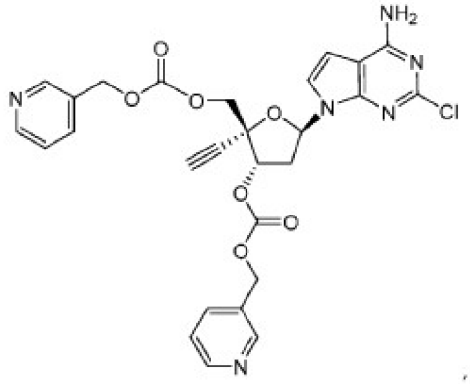


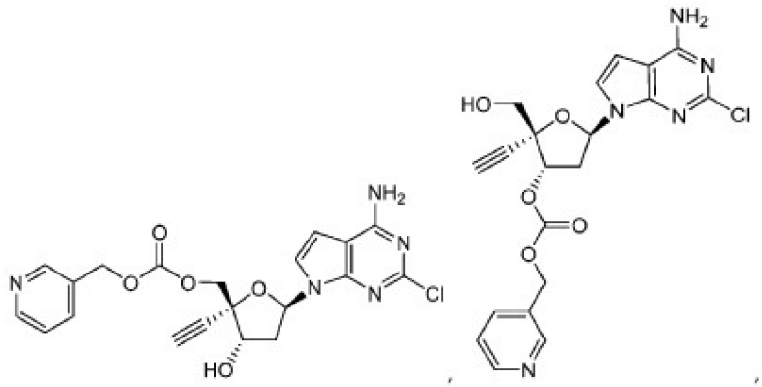


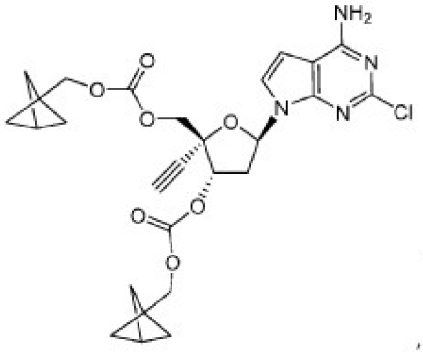


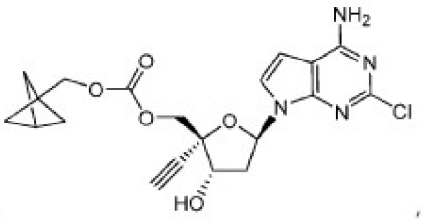


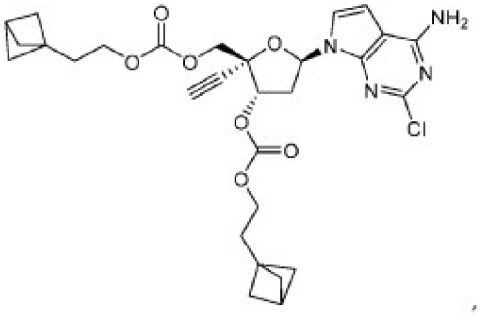


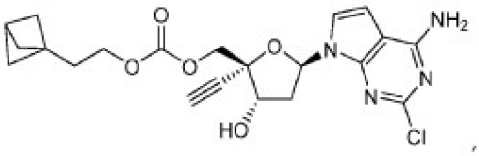


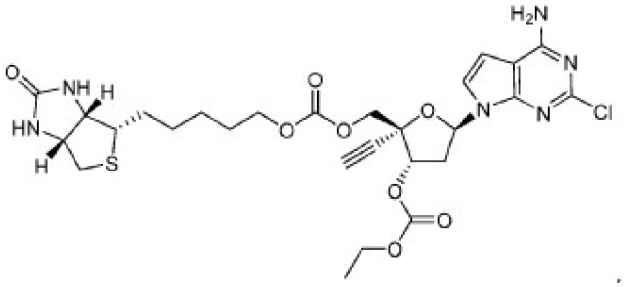


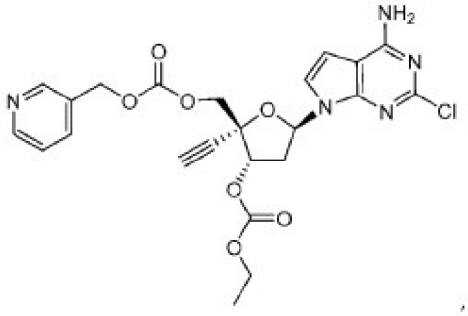


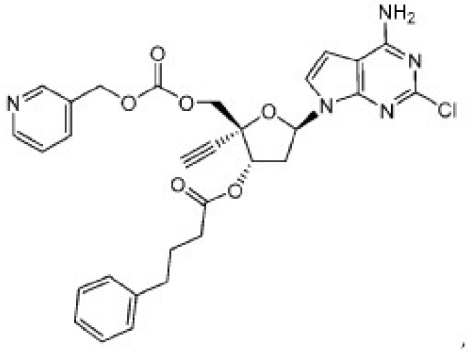


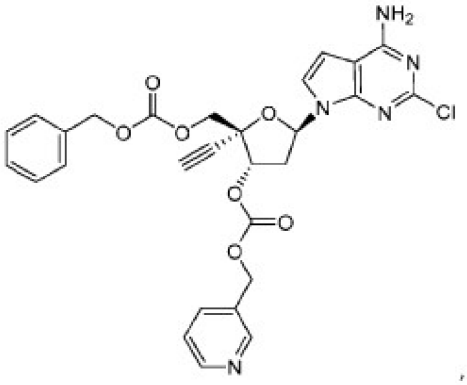


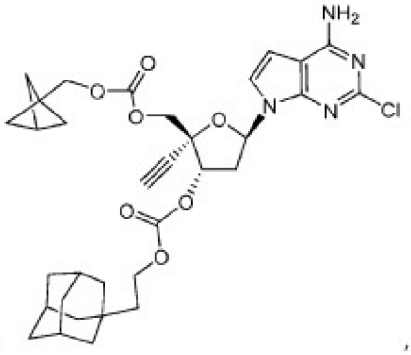


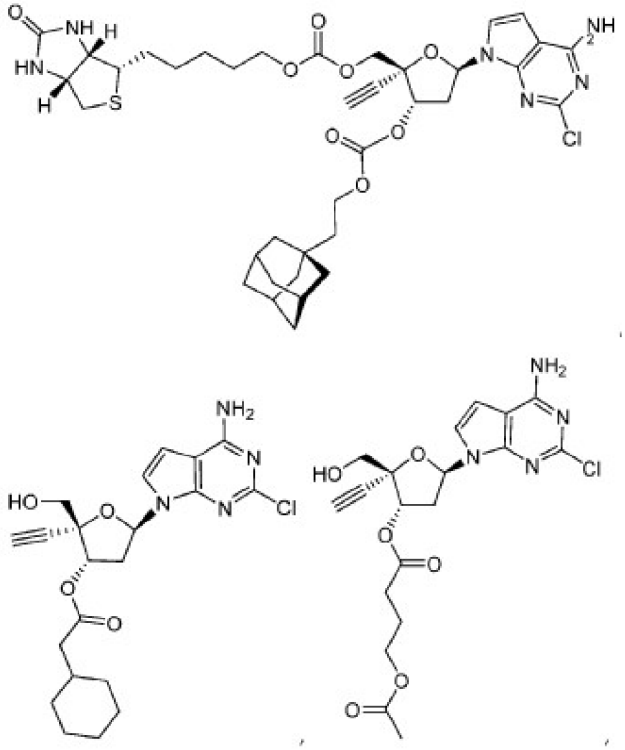


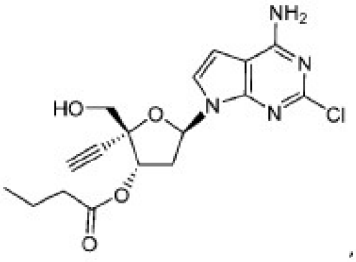


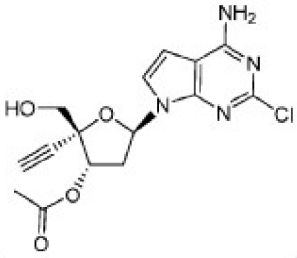


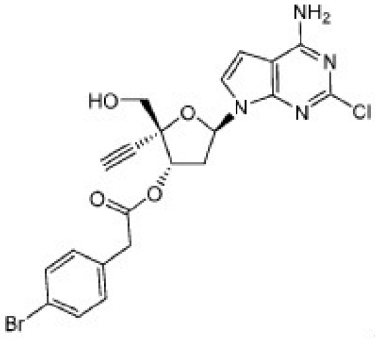


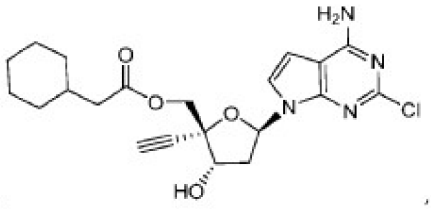


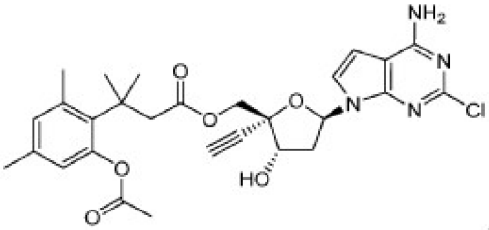


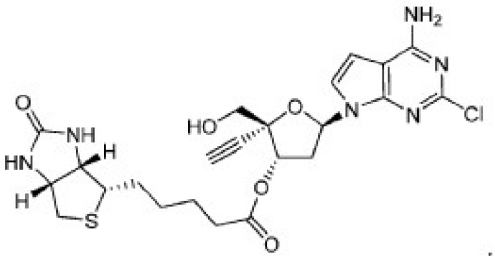


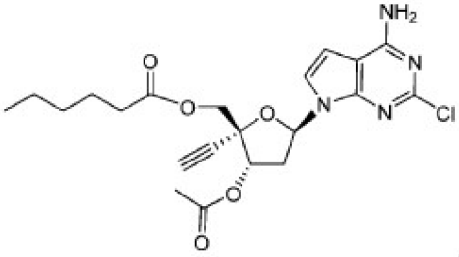


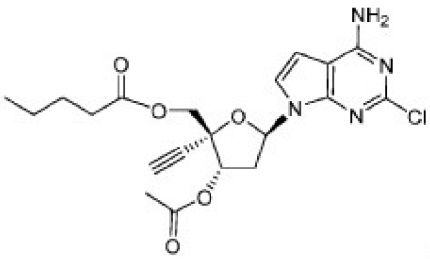


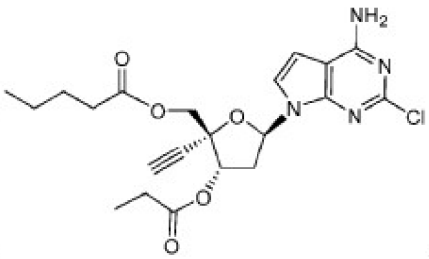


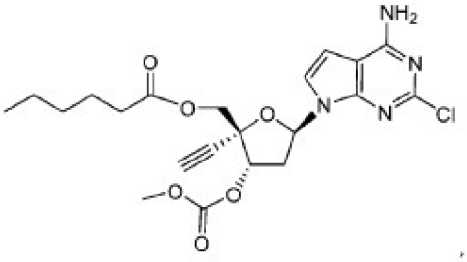


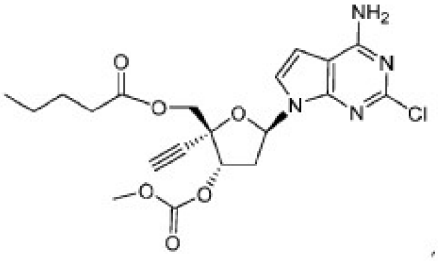


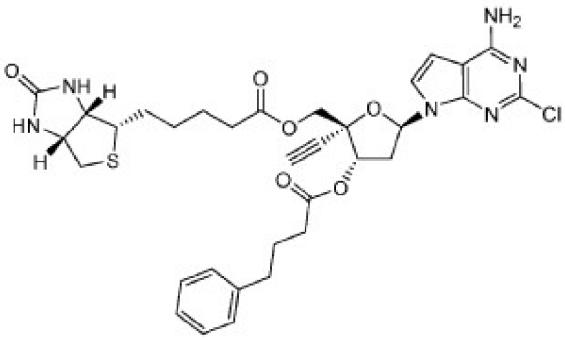


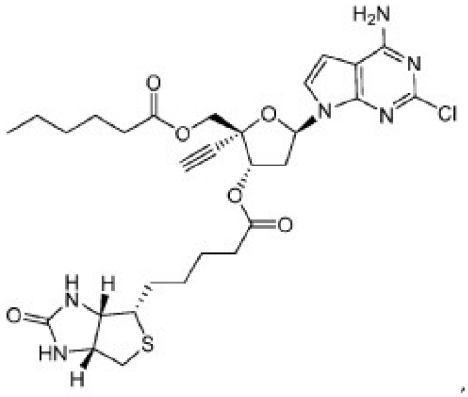


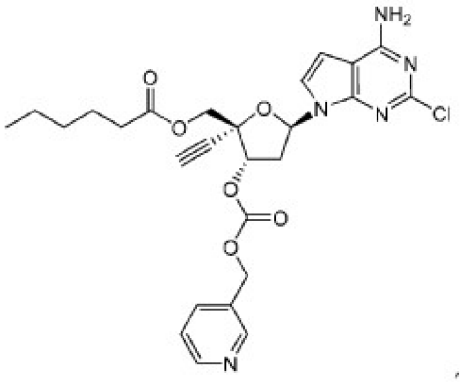


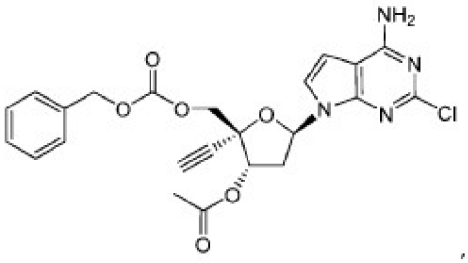


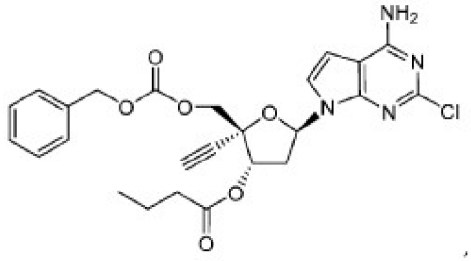


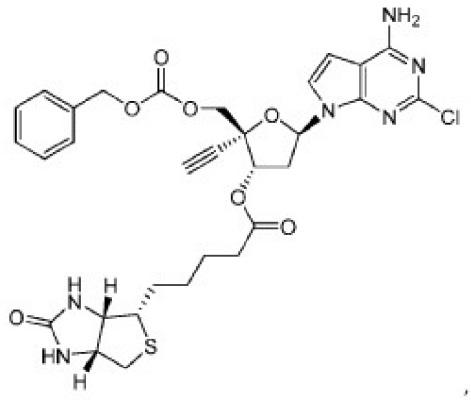


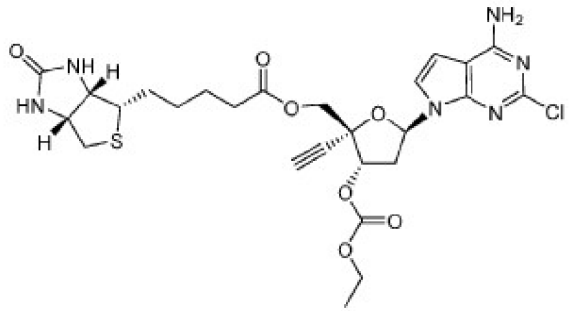


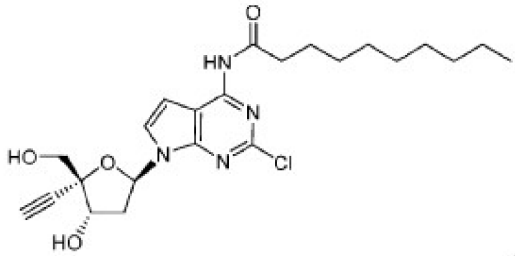


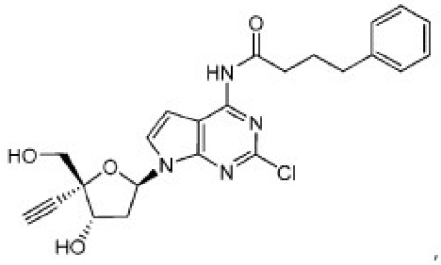


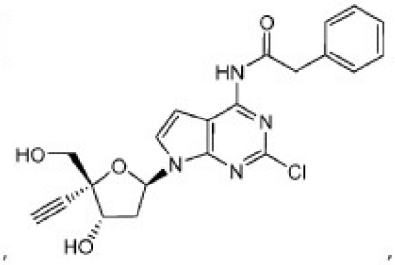


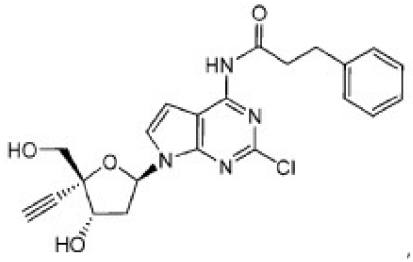


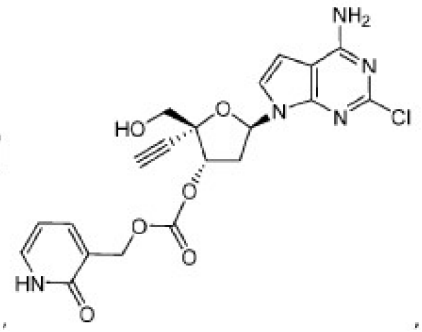


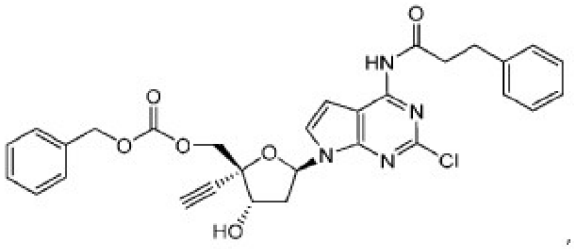


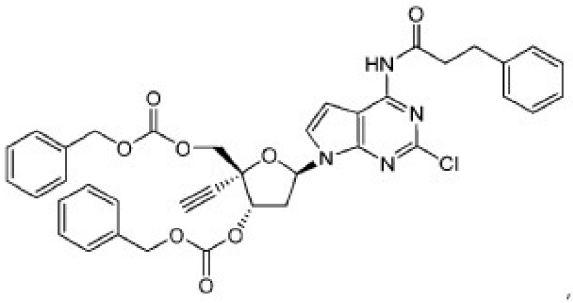


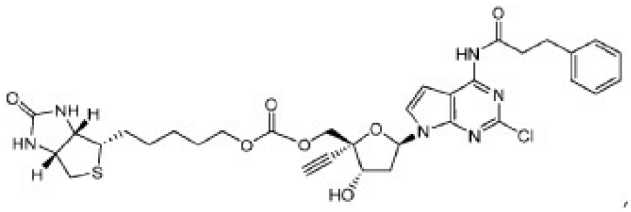


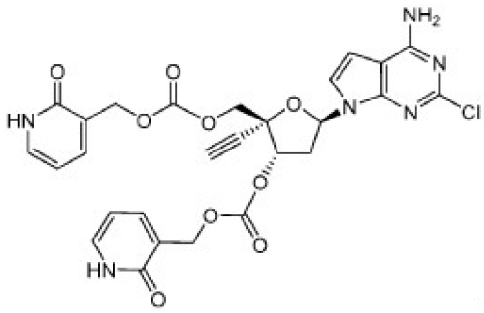


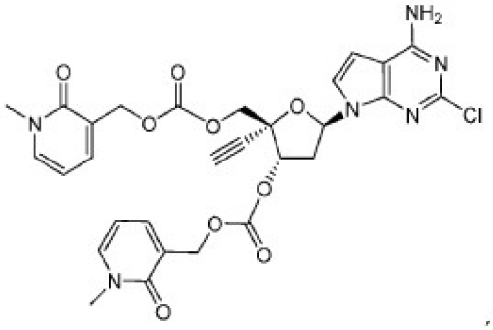


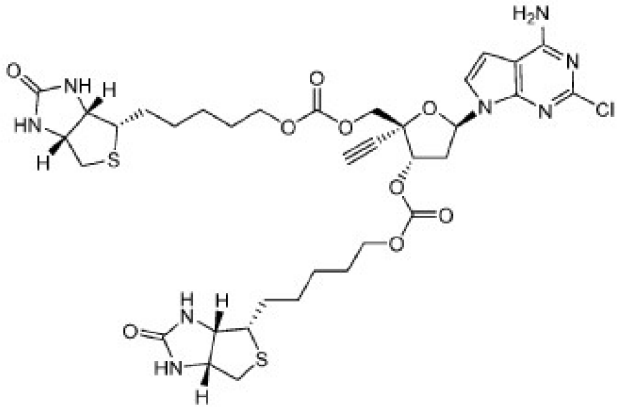


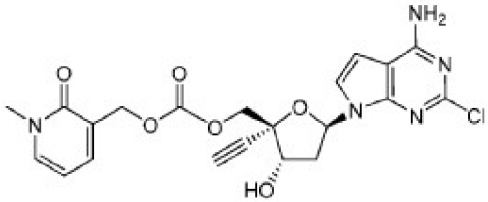


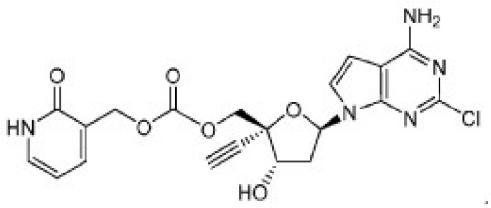


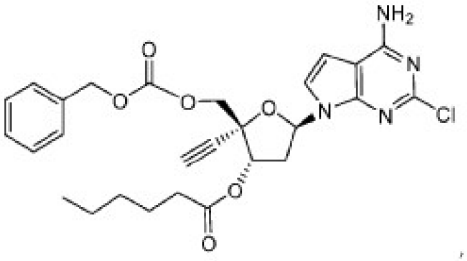


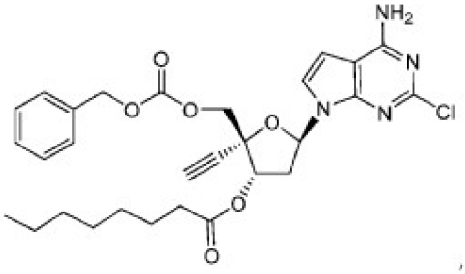


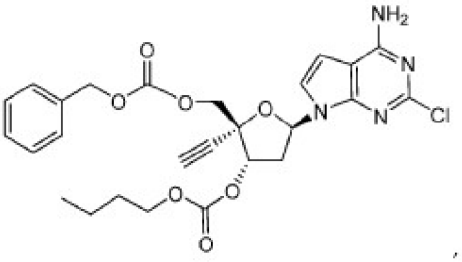


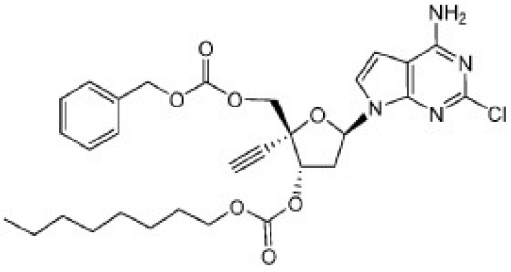


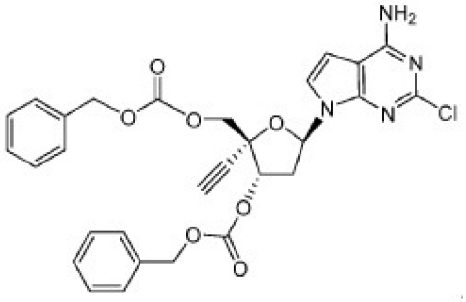


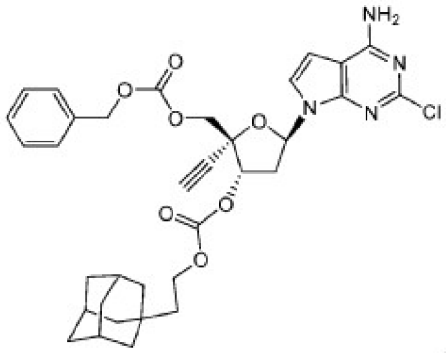


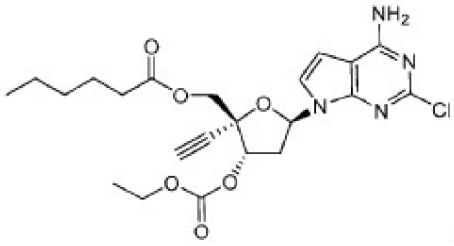


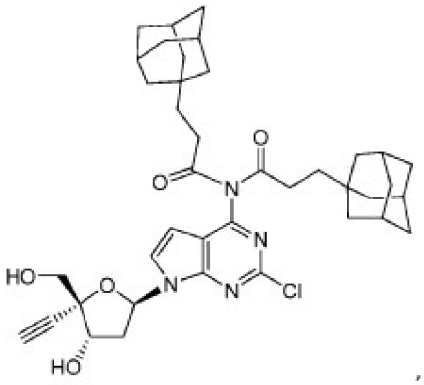


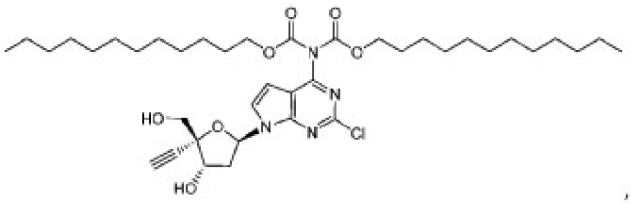


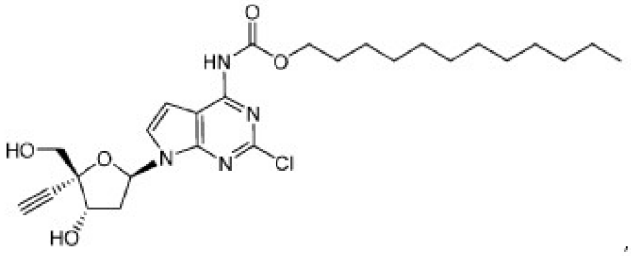

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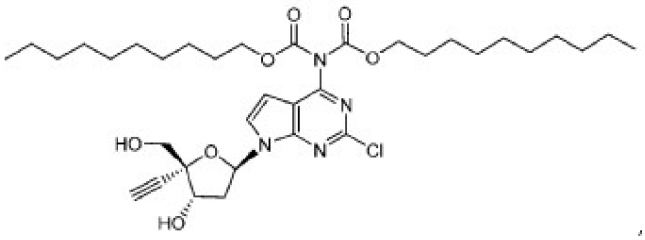

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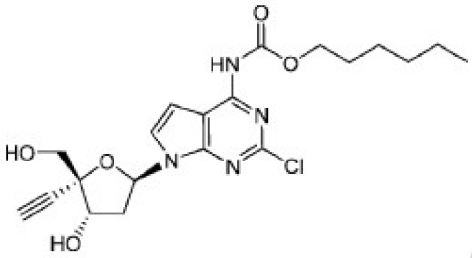

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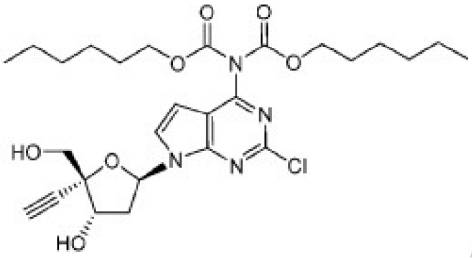


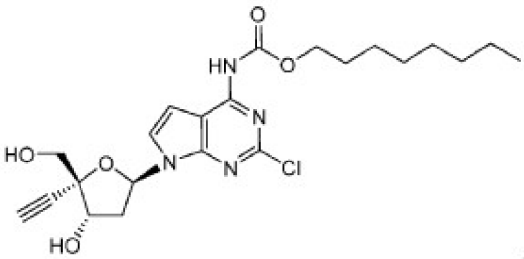


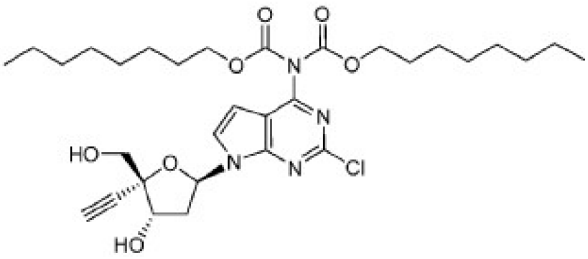


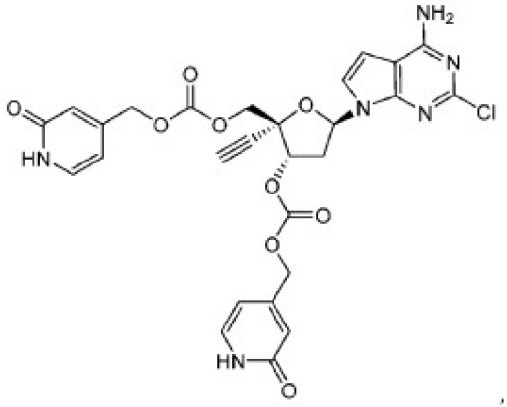
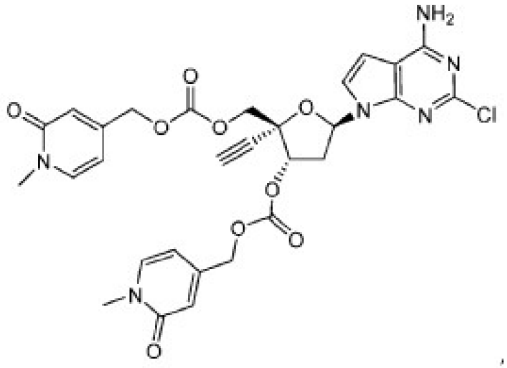
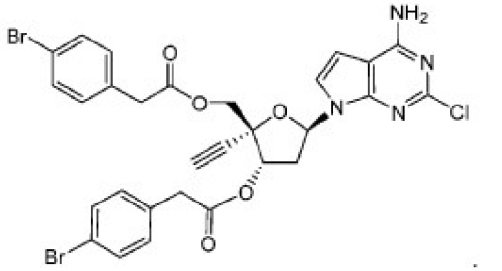






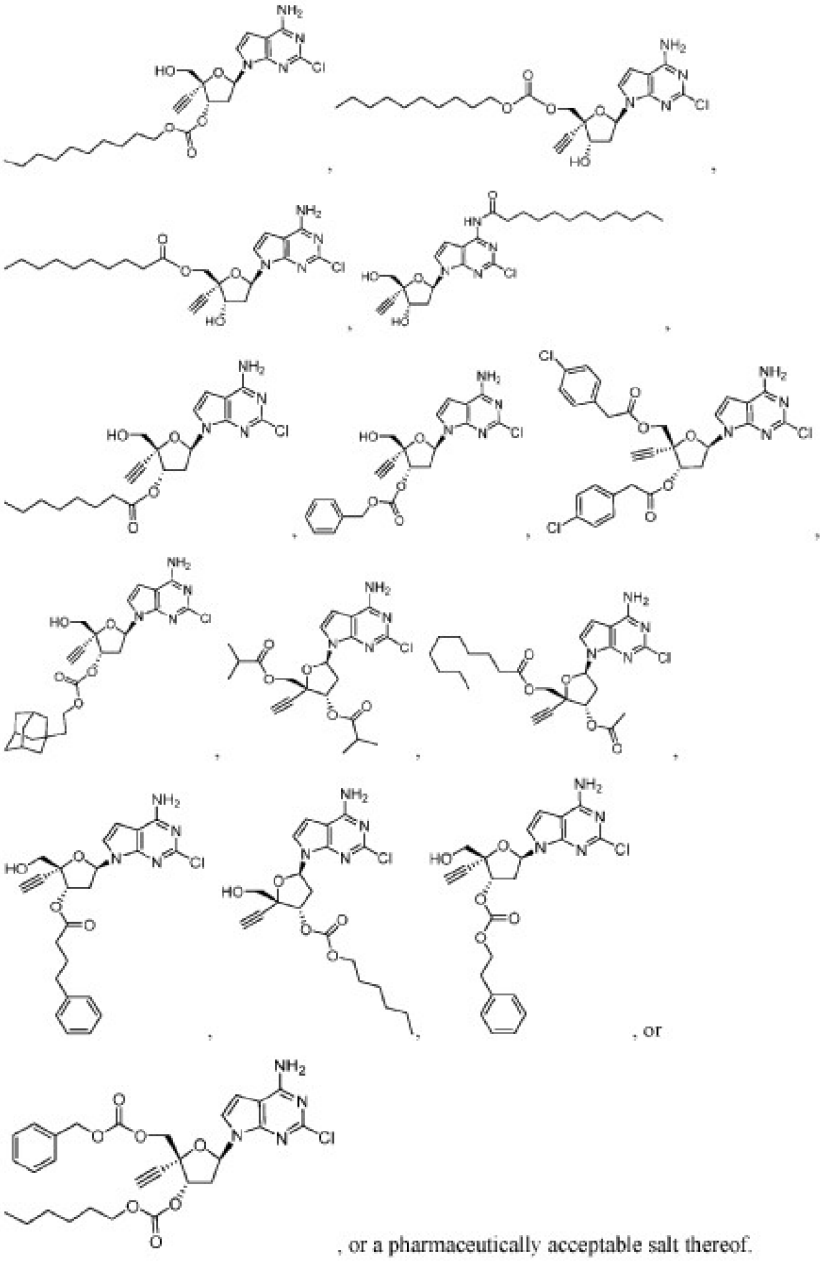




or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1-9 having the structure:



, or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound or salt of any one of claims 1-11, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, wherein the composition is injectable, or adapted for injection.

14. A pharmaceutical composition of claim 12 or 13, further comprising one or more additional therapeutic agents selected from the group consisting of lenacapavir, raltegravir, lamivudine, abacavir, ritonavir, dolutegravir, darunavir, atazanavir, emtricitabine, tenofovir, elvitegravir, rilpivirine, lopinavir, doravirine and islatravir.

15. A method for the inhibition of HIV reverse transcriptase in a subject in need thereof which comprises administering to the subject an effective amount of the compound or salt of any one of claims 1-11, or the pharmaceutical composition of any one of claims 12-14.

16. A method for the treatment of infection by HIV or the treatment, prophylaxis, or delay in onset or progression of AIDS in a subject in need thereof, comprising administering to the subject an effective amount of the compound or salt of any one of claims 1-11, or the pharmaceutical composition of any one of claims 12-14.

17. The method of claim 16 further comprising administering to the subject one or more additional therapeutic agents selected from the group consisting of lenacapavir, raltegravir, lamivudine, abacavir, ritonavir, dolutegravir, darunavir, atazanavir, emtricitabine, tenofovir, elvitegravir, rilpivirine, lopinavir, and doravirine, wherein the amounts administered of the compound or salt of any one of claims 1-11 and the one or more additional therapeutic agents are together effective to treat infection by HIV or to treat, prevent or delay the onset or progression of AIDS.

18. The method of claim 17, wherein the additional therapeutic agent is lenacapavir.

19. The method of any one of claims 15-18, wherein the method comprises administering the compound or salt in accordance with a dosing interval range from about once per month to about once per every twelve months.

20. The method of claim 19, wherein the dosing interval range is about once per every three months, once per every six months, or once per every twelve months.

21. The compound or salt of any one of claims 1-11, or the pharmaceutical composition of any one of claims 12-14, for use in the preparation of a medicament for the inhibition of HIV reverse transcriptase, for the treatment or prophylaxis of infection by HIV, or for the treatment, prophylaxis, or delay in the onset or progression of AIDS in a subject in need thereof.

22. The compound or salt of any one of claims 1-11, or the pharmaceutical composition of any one of claims 12-14, for use in therapy.