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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	36	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issu number(s), publisher, city and/or country where published.	T ²
		MOURIER, et al., "Enantioselective synthesis and biological evaluation of 5-o-carboranyl-pyrimidine-nucleosides," Bioorganic & Medicinal Chemistry, vol. 7, pp. 2759-2766, (1999).	
		MURAKAMI et al., "Mechanism of Activation of beta-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine and Inhibition of hepatitis C Virus NS5B RNA Polymerase," Antimicrobial Agents and Chemotherapy, vol. 51, no. 2, pp. 503-509 (Feb. 2007).	
		MURAKAMI et al., "The Mechanism of Action of beta-D-2'-Deoxy-2'-Fluoro-2'-C-Methylcytidine Involves a Second Metabolic Pathway Leading to beta-D-2'-Deoxy-2'-Fluoro-2'-C-Methyluridine 5'-Triphosphate, a Potent Inhibitor of the Hepatitis C Virus RNA-Dependent RNA Polymerase," Antimicrobial Agents and Chemotherapy, vol. 52, no. 2, pp. 458-464 (2008).	
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		MURAKAMI, E., et al., "The Mechanism of Action of beta-D-2'-Deoxy-2'-fluoro-2'-C-methylcytidine Involves a Second Metabolic Pathway Leading to beta-D-2'-Deoxy-2'-fluoro-2'-C-methyluridine 5'-Triphosphate, a Potent Inhibitor of the HCV RNA-Dependent RNA Polymerase," 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland (Sep. 2007).	
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		NI et al., "Progress and development of small molecule HCV antivirals," Current Opinion in Drug Discovery & Development, vol. 7, no. 4, pp. 446-459 (2004).	

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		NIFANTYEV et al., "Synthesis and Structure of Some Stable Phospholane-Phospholanes," Phosphorus, Sulfur, and Silicon, vol. 113, pp. 1-13 (1996).	
		North et al., Hepatitis C treatment and SVR: the gap between clinical trials and real-world treatment aspirations. Gen Hosp Psychiatry. Mar-Apr 2013;35(2):122-128. doi: 10.1016/j.genhosppsych.2012.11.002. Epub 2012 Dec 6.	
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		Office Action and Search Report for Chinese Patent Application No. 201811280064.6 dated September 9, 2019. 21 pages	
		Office Action and Search Report for Chinese Patent Application No. 201811348434.5 dated October 8, 2019. 29 pages	
		Office Action dated 2015-05-29 for Argentina Appl. No. 120100340.	
		Office Action dated 2015-06-15 for Australian Appl. No. 2014215983.	
		Office Action dated 2016-02-24 for European Appl. No. 14179358.8.	

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		Office Action dated 2016-03-02 for Argentina Appl. No. 20080101286.	
		Office Action dated 2016-03-04 for Chinese Appl. No. 201410569402.3.	
		Office Action dated 2016-04-06 for Taiwan Appl. No. 097111505.	
		Office Action dated 2016-07-05 for Japanese Appl. No. 2015-139458.	
		Office Action dated 2016-10-04 for Argentina Appl. No. 120100340.	
		Office Action dated 2016-11-15 for Australian Appl. No. 2016213882.	
		Office Action dated 2017-01-30 for Russian Appl. No. 2012152811.	
		Office Action dated 2017-03-14 for Chinese Appl. No. 201410569402.3.	
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		Office Action dated 2017-06-15 for Malaysian Appl. No. PI2013700240.	
		Office Action dated 2017-06-26 for European Appl. No. 14169060.2.	
		Office Action dated 2017-06-28 for European Appl. No. 14151876.1.	
		Office Action dated 2017-06-28 for European Appl. No. 14179358.8.	
		Office Action dated 2017-06-28 for European Appl. No. 14179593.0.	
		Office Action dated 2017-08-15 for Japanese Appl. No. 2017-000051.	
		Office Action dated 2017-10-25 for Brazilian Appl. No. PI0809654-6.	
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		Office Action for Colombian Application No. 09-120.744A dated 06/25/2014.	
		Office Action for European Patent Application No. 14151876.1 dated December 20, 2018. 4 pages	
		Office Action for European Patent Application No. 14169060.2 dated December 20, 2018. 5 pages	
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		Opposition by Generics [UK] Ltd (trading as Mylan) to European Application No. 08732818.3 dated 02/19/2015.	
		Opposition by Indian Pharmaceutical Alliance to Indian Application No. 3658/KOLNP/2009 dated 02/17/2015.	
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		Opposition by Pharmaceutical Works Polpharma S.A. to European Application No. 08732818.3 dated 02/19/2015.	

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		Opposition by Stada Arzneimittel AG to European Application No. 08732818.3 dated 02/19/2015.	
		Opposition by Teva Pharmaceutical Industries to European Application No. 08732818.3 dated 02/10/2015.	
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SMRH:4831-9482-4419.1

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	46	of	51	Attorney Docket Number	37JD-199059-US13

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		SHIH et al., "Preparation and Structures of 2-Dimethylamino-4-phenyl-1,3,2-dioxaphosphorinane-2-oxides," Bull. Inst. Chem., Acad. Sin., vol. 41, pp. 9-16, (Mar. 1994).	
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		SICCARDI et al., "Stereospecific chemical and enzymatic stability of phosphoramidate triester prodrugs of d4T in vitro," European Journal of Pharmaceutical Sciences, vol. 22, pp. 25-31 (2004).	
		SIDDIQUI et al., "Design and Synthesis of Lipophilic Phosphoramidate d4T-MP Prodrugs Expressing High Potency Against HIV in Cell Culture: Structural Determinants for in Vitro Activity and QSAR," J. Med. Chem., vol. 42, no. 20, pp. 4122-4128 (1999).	
		SIDDIQUI et al., "Enhancing the Aqueous Solubility of d4T-based Phosphoramidate Prodrugs," Bioorg. and Med. Chem. Lett., vol. 10, pp. 381-384 (2000).	
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		Sofia et al., Discovery of a beta-D-2'-Deoxy-2'-alpha-fluoro-2'-beta-C-methyluridine Nucleotide Prodrug (PSI-7977) for the Treatment of Hepatitis C Virus. J. Med. Chem. 2010, 53, 19, 7202-7218.	

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		STUYVER et al., "Inhibition of the Subgenomic Hepatitis C Virus Replicon in Huh-7 Cells by 2'-Deoxy-2'-Fluorocytidine," Antimicrobial Agents and Chemotherapy, vol. 48, no. 2, pp. 651-654 (2004).	

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				Art Unit	1623
				Examiner Name	Not Yet Assigned
Sheet	48	of	51	Attorney Docket Number	37JD-199059-US13

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		STUYVER et al., "Ribonucleoside Analogue that Blocks Replication of Bovine Viral Diarrhea and Hepatitis C Viruses in Culture," Antimicrobial Agents and Chemotherapy, vol. 47, no. 1, pp. 244-254 (2003).	
		Subsequent Substantive Examination Report for Philippines Application No. 1/2009/501847 dated 11/10/2014.	
		Substantive Examination Report for Malaysian Patent Application No. PI2013700238 dated March 6, 2020. 3 pages	
		Substantive Examination Report for Malaysian Patent Application No. PI2013700240 dated August 15, 2019. 3 pages	
		Substantive Examination Report for Philippines Patent Application No. 1-2014-502771 dated November 28, 2019. 5 pages	
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		UCKUN et al., "In Vivo Pharmacokinetics and Toxicity Profile of the Anti-HIV Agent Stampidine in Dogs and Feline Immunodeficiency Virus-infected Cats," <i>Arzneim.-Forsch./Drug Res.</i> , vol. 56, no. 2a, pp. 176-192 (2006).	
		VALETTE et al., "Decomposition Pathways and in Vitro HIV Inhibitory Effects of IsoddA Pronucleotides: Toward a Rational Approach for Intracellular Delivery of Nucleoside 5'-Monophosphates," <i>J. Med. Chem.</i> , vol. 39, no. 10, pp. 1981-1990 (1996).	
		VAN ROMPAEY, et al., "Mycobacterium tuberculosis thymidine monophosphate kinase inhibitors: biological evaluation and conformational analysis of 2'-and 3'-modified thymidine analogues," <i>Eur. J. Org. Chem.</i> , pp. 2911-2918, (2003).	
		VANHEUSDEN et al., "Discovery of bicyclic thymidine analogues as selective and high-affinity inhibitors of mycobacterium tuberculosis thymidine monophosphate kinase," <i>J. Med. Chem.</i> , vol. 47, pp. 6187-6194, (2004).	
		Vanheusden et al., Synthesis and evaluation of thymidine-5'-O-monophosphate analogues as inhibitors of Mycobacterium tuberculosis thymidylate kinase. <i>Bioorganic & Medicinal Chemistry Letters</i> , vol. 12, pp. 2695-2698 (2002).	
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		Walker et al., Promising candidates for the treatment of chronic hepatitis C. <i>Expert Opinion on Investigational Drugs</i> , vol. 12, no. 8, pp. 1269-1280 (2003).	

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		WARRENER et al., "Pestivirus NS3 (p80) Protein Possesses RNA Helicase Activity," J. Virol., vol. 69, no. 3, pp. 1720-1726 (1995).	
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		WISKERCHEN et al., Pestivirus Gene Expression: Protein p80 of Bovine Viral Diarrhea Virus Is a Proteinase Involved in Polyprotein Processing, Virology, vol. 184, pp. 341-350 (1991).	
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				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
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Sheet	51	of	51	Attorney Docket Number	37JD-199059-US13

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		Xu et al., "Bovine Viral Diarrhea Virus NS3 Serine Proteinase: Polypeptide Cleavage Sites, Cofactor Requirements, and Molecular Model of an Enzyme Essential for Pestivirus Replication," J. Virol., vol. 71, no. 7, pp. 5312-5322 (1997).	
		YUAN et al., "Expression, Purification, and Partial Characterization of HCV RNA Polymerase," Biochemical and Biophysical Research Communications, vol. 232, no. 1, pp. 231-235 (1997).	
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		ZON, G., "4 Cyclophosphamide Analogues," Progress in Medicinal Chemistry, vol. 19, pp. 205-246 (1982).	

Examiner Signature	/PATRICK T LEWIS/	Date Considered	04/06/2022
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237
117796	7590	04/12/2022		
Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626			EXAMINER LEWIS, PATRICK T	
			ART UNIT	PAPER NUMBER
			1623	
			NOTIFICATION DATE	DELIVERY MODE
			04/12/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SheppardMullin_Pair@firsttofile.com
ipdocketing@gilead.com
svipdocketing@sheppardmullin.com

Office Action Summary	Application No. 17/077,267	Applicant(s) Du et al.	
	Examiner PATRICK T LEWIS	Art Unit 1623	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

- 5) ☒ Claim(s) 13-19 is/are pending in the application.
- 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 13-19 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- Certified copies:**
- a) ☐ All b) ☐ Some** c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 3) ☐ Interview Summary (PTO-413) |
| | Paper No(s)/Mail Date ____. |
| 2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) | 4) ☐ Other: ____. |
| Paper No(s)/Mail Date <u>04192021</u> . | |

U.S. Patent and Trademark Office

PTOL-326 (Rev. 11-13)

Office Action Summary

Part of Paper No./Mail Date 20220407

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 112

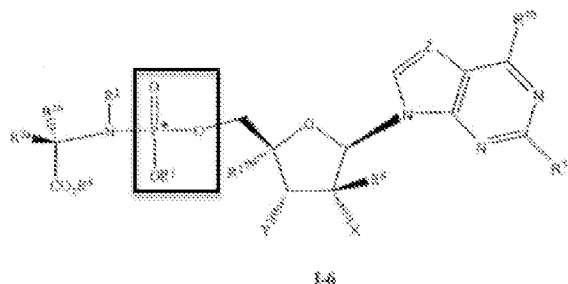
2. The following is a quotation of 35 U.S.C. 112(d):

(d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

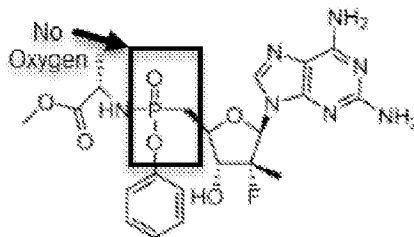
The following is a quotation of pre-AIA 35 U.S.C. 112, fourth paragraph:

Subject to the following paragraph [i.e., the fifth paragraph of pre-AIA 35 U.S.C. 112], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

3. Claims 17-19 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 13 is drawn to a compound of formula I-6 wherein the phosphorous moiety is connected to the sugar moiety via oxygen.



In claims 17-19, which ultimately depend from claim 13, the compound does not read upon a compound wherein the phosphorous moiety is connected to the sugar moiety via oxygen.



Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103

4. In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.
5. The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

8. Claims 13-16 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clark WO 2005/003147 A2 (Clark) and Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (Perrone) in combination.

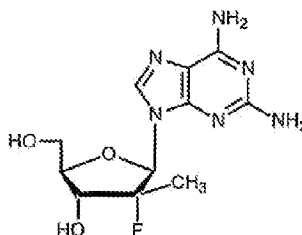
Claims 13-16 are drawn to a compound of formula I-6.

Clark is drawn to (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleosides having the natural β -D configuration and methods for the treatment of Flaviviridae infections, especially hepatitis C virus (HCN) (page 1, lines 6-8). The antivirally effective nucleoside

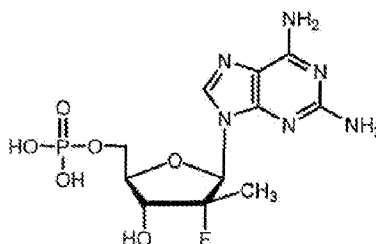
is a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside (β -D or β -) or its pharmaceutically acceptable salt or prodrug thereof of the general formula:



See page 31, line 25 to page 33, line 17. In one embodiment, a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside, its pharmaceutically acceptable salt or product thereof is provided by the structure:



See page 42, lines 2-5. Non-limiting examples of phosphoric acid derivatives include:



See page 45, line 1. Clark also contemplated wherein the N-4 amino group on a phosphate nucleoside derivative can be replaced with H, F, Br or I (page 45, lines 2-6). Clark teaches that any of the nucleosides described therein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the

properties of the nucleoside (page 46, lines 16-25). A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide.

Thus, Clark teaches or reasonably suggests a nucleoside or monophosphate thereof corresponding to instant formula I-6 wherein: $X = F$; $Y = OH$; $Z = N$; $R^5 = H$; $R^6 = CH_3$; $R^{10} = NH_2, H, F, Br \text{ or } I$; and $R^{11} = NH_2$. Clark further reasonably suggests nucleotide prodrugs (protides) thereof.

Clark differs from the instantly claimed invention in that Clark does not explicitly teach or exemplify a protide of a (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl nucleoside in a singular embodiment; however, this deficiency would have been obvious in view of the teachings of Perrone.

Perrone is drawn to the application of phosphoramidate ProTide technology to the ribonucleoside analogue 4'-azidouridine to generate novel antiviral agents for the inhibition of hepatitis C virus (HCV) (Abstract). A number of compounds showed sub-micromolar inhibition of HCV in cell culture without detectable cytotoxicity. These results confirm that phosphoramidate ProTides can deliver monophosphates of ribonucleoside analogues and suggest a potential path to the generation of novel antiviral agents against HCV infection. Perrone's aryloxy phosphoramidate ProTide approach allows bypass of the initial kinase dependence by intracellular delivery of the monophosphorylated nucleoside analogue as a membrane permeable "ProTide" form (page 1840). This technology greatly increases the lipophilicity of the nucleoside monophosphate analogue with a consequent increase of membrane permeation and intracellular availability. Previously the approach was successfully demonstrated with the aryloxy-

phosphoramidate derivatives of ddA, d4T, LCd4A, and d4A. These nucleotide monophosphate analogues were shown to exhibit greatly enhanced activity against HIV compared to the parent nucleoside analogues in vitro.

As shown in Table 1, L-alanine derivatives represented a series of active antiviral phosphoramidates (**11-17**) (pages 1842-1843). Low or sub-micromolar activity was noted in marked contrast to the inactive nucleoside parent (**1**).

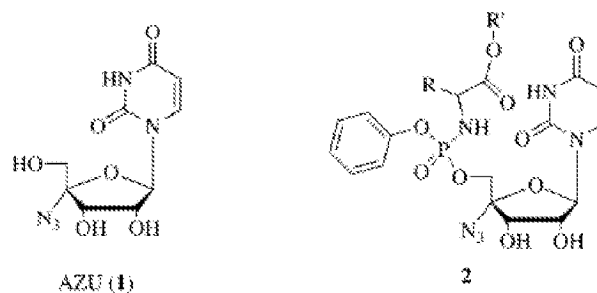


Figure 1. Structure of AZU and its corresponding phenyl-phosphoramidate ProTide.

Table 1. Anti HCV Activity and Cytotoxicity Data for (**1**) and Phenyl Phosphoramidate Nucleotide Analogues

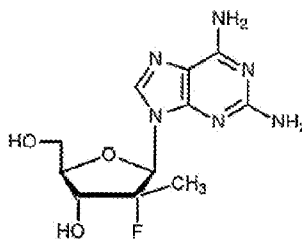
compound	amino acid	ester	EC ₅₀ (μM)	CC ₅₀ (μM)
11	L-Ala	Me	3.1	>100
12	L-Ala	Et	1.3	>100
13	L-Ala	Bu	1.2	>100
14	L-Ala	2-Bu	0.63	>100
15	L-Ala	iPr	0.77	>100
16	L-Ala	tBu	5.1	>100
17	L-Ala	Bn	0.61	>100
18	Me ₂ Gly	Et	10.3	>100
19	Me ₂ Gly	Bn	3.4	>100
20	αPntGly	Et	>100	>100
21	αPntGly	Bn	<100	>100
22	Phe	Et	1.37	>100
23	Phe	Bn	<100	>100
24	Val	Bn	<100	>100
25	Gly	Bn	1.6	>100
26	D-Ala	Bn	1.2	>100
27	Leu	Et	2.3	>100
28	Pro	Et	6.0	>100
29	Met	Et	14	>100
30	N-MeGly	Et	>100	>100
31	EtGlu	Et	>100	>100
32	β-Ala	Et	>100	>100
4-azido-2-deoxyadenosine (1)	—	—	>100	>100

Thus, Perrone teaches or reasonably suggests a phosphoramidate moiety corresponding to instant compound I-6 wherein: R^1 = phenyl; R^2 = H; R^{3a} = H; R^{3b} = methyl; and R^4 = methyl, ethyl, butyl, 2-butyl, or isopropyl.

In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983).

In the instant case, the references may be combined to show obviousness because Clark and Perrone are each drawn to nucleic acids and their use for treating HCV. They are from the same field of endeavor, and/or are reasonably pertinent to a compound of instant formula I-6.

In the absence of unexpected results, it would have been obvious to one of ordinary skill in the art at the time of the invention to provide the anti-HCV compounds of Clark, e.g.



as a prodrug wherein the H of the 5'-OH moiety is replaced by a phosphoramidate moiety of Perrone. One would have been motivated to do so in order to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside as suggested by Clark. One would have had a reasonable expectation of success in view of

Perrone's teaching that by incorporating such a moiety low or sub-micromolar activity against HCV was achieved.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

All of the instant limitations are taught by the combination of Clark and Perrone. A person of ordinary skill in the art would have had a reason to combine the teachings of Clark and Perrone. A person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of Clark and Perrone. Thus, claims 143-16 would have been obvious based on the preponderance of the evidence.

Conclusion

9. Claims 13-19 are pending. Claims 13-19 are rejected. No claims are allowed.

Contacts

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK T LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached Monday to Friday, 10 AM to 4 PM EST (Maxi Flex).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an

interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

/PL/

FILE 'REGISTRY' ENTERED AT 19:00:17 ON 06 APR 2022
L1 STRUCTURE UPLOADED
L2 2 S L1 SSS SAM
L3 14 S L1 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 19:08:49 ON 06
APR 2022
L4 3 S L3

FILE 'REGISTRY' ENTERED AT 19:18:38 ON 06 APR 2022
L5 STRUCTURE UPLOADED
L6 50 S L5 SSS SAM
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APR 2022
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L9 STRUCTURE UPLOADED
L10 4 S L9 SSS SAM
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L12 7 S L11

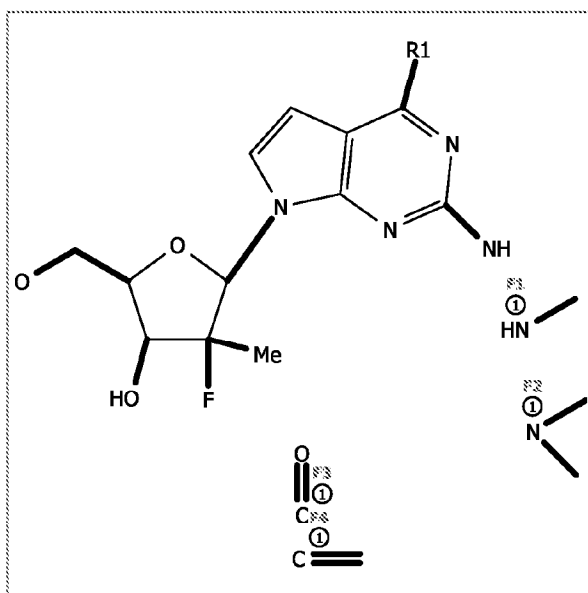
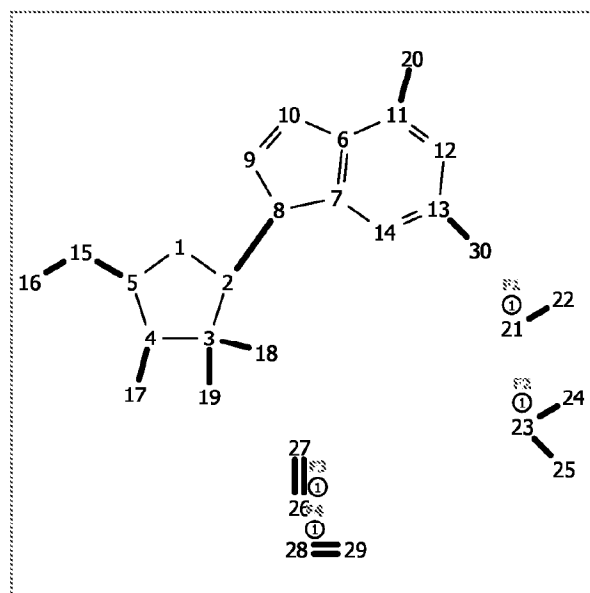
Structure Details

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



R-group Definitions

R-group	Values
R1	H, X, OH, NH2, F1, F2, F3, F4

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Ring				
15, 16, 19, 22, 23, 24, 25, 26, 27, 28, 29	Chain				

Bond Attributes

Bond	Type	Value
6-11, 6-7, 11-12, 12-13, 13-14, 14-7	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1, 7-8, 8-9, 9-10, 10-6	Ring	Exact/Normalized
28-29	Chain	Exact
3-18, 3-19, 4-17, 5-15, 8-2, 11-20, 13-30, 15-16, 21-22, 23-24, 23-25, 26-27	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Atom	Limited
15, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30	Class	Limited

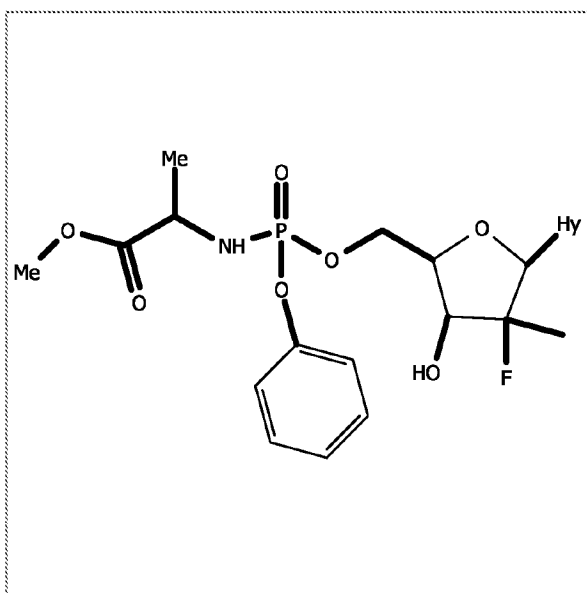
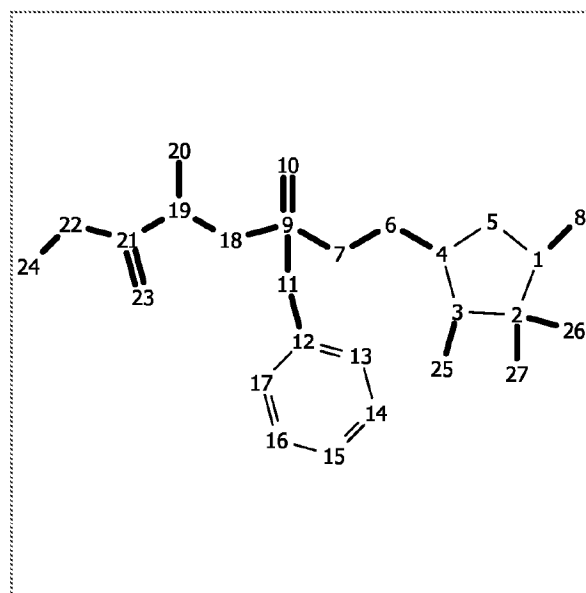
Structure Details (17077267-str5)

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 12, 13, 14, 15, 16, 17	Ring				
6, 7, 9, 10, 11, 19, 21, 22, 23, 26, 27	Chain				

Bond Attributes

Bond	Type	Value
12-13, 13-14, 14-15, 15-16, 16-17, 17-12	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
2-26, 2-27, 4-6, 19-20, 19-21, 22-24	Chain	Exact
1-8, 3-25, 6-7, 7-9, 9-10, 9-11, 9-18, 11-12, 18-19, 21-22, 21-23	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17	Atom	Limited
6, 7, 9, 10, 11, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Class	Limited

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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Patrick T. Lewis
Sheet	1	of	1	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2004113360	12-29-2004	G NAUCHNY TS VIRUSOLOGII BIO		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Blanver's Third-party Opinion Brief in Brazilian Patent Application No. PI0809654-6 dated December 18, 2020. 26 pages	
		Erti et al. A comparative study of the in vitro and in vivo antiviral activities of acyclovir and penciclovir. Antiviral Chemistry & Chemotherapy. 1995, 6(2), 89-97, page 89, left column, "Summary", pages 89-93, section "Results", pages 93,94, section "Discussion".	
		Office Action and Search Report for Chinese Patent Application No. 201811280509.0 dated March 3, 2022. 22 pages	
		Office Action for Chinese Patent Application No. 201811280064.6 dated April 2, 2022. 13 pages	
		Office Action for Chinese Patent Application No. 201811348434.5 dated April 2, 2022. 12 pages	
		Official Action for Argentinian Patent Application No. 20170103608 dated January 26, 2022. 6 pages	
		Official Action for Russian Patent Application No. 2018103329 dated May 24, 2021. 26 pages	
		Opposition by Mr. Yellajyosula Lakshmi Narasimha Murthy dated October 28, 2021. 17 pages	
		Rejection Resolution for Argentinean Patent Application No. 20120100340 dated May 31, 2022. 16 pages	

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language translation is attached.

SMRH:4859-2833-9753.1

Electronic Patent Application Fee Transmittal				
Application Number:		17077267		
Filing Date:		22-Oct-2020		
Title of Invention:		NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		
First Named Inventor/Applicant Name:		Jinfa Du		
Filer:		Joy Lynn Bala Nemirow/Joannah Lalueces		
Attorney Docket Number:		37JD-199059-US13		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Miscellaneous:				
SUBMISSION- INFORMATION DISCLOSURE STMT	1806	1	260	260
Total in USD (\$)				260



Espacenet

Bibliographic data: WO2004113360 (A1) — 2004-12-29

**PHOSPHOROMIDATES OF NUCLEOSIDE ANALOGUES-REPRODUCTION
INHIBITORS FOR HUMAN IMMUNODEFICIENT VIRUS**

Inventor(s): POKROVSKY ANDREI GEORGIEVICH [RU]; PRONYAEVA
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SHIPITSIN, ALEKSANDR VALEREVICH, ; SHIROKOVA, ELENA
ANATOLEVNA, ; ZAKIROVA, NATALYA FANISOVNA)

Classification: - international: **A61P31/18; C07H19/10;** (IPC1-7): A61P31/18,
C07H19/10
- cooperative: **A61P31/18 (EP); C07H19/10 (EP)**

Application WO2003RU00514 20031121 [Global Dossier](#)
number:

Priority [RU20030119415 20030626](#)
number(s):

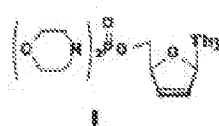
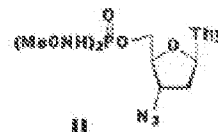
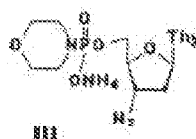
Also [RU2243972 \(C1\)](#)
published as:

Abstract of WO2004113360 (A1)

The invention relates to novel biologically active derivatives of 5'-phosphate 3'-azido-3'-deoxythymidine and of 2',3'-dideoxy-2',3'-didehydrothymidine and can be used in the

form of antiviral agents, first and foremost against a human immunodeficient virus (HIV). Said invention makes it possible to develop and use novel compounds which are resistant with respect to the action of dephosphorylation enzymes, capable to penetrate inside a cell and exhibit selective activity for suppressing DNA biosynthesis which is catalysed by the HIV reverse transcriptase. Said technical

result is achieved by the novel inventive compounds, i.e. phosphorimidates of nucleoside analogues comprising 5'-phosphodimotpholydate of 2',3'-dideoxy-2',3'-didehydrothymidine (formula I) and phosphoromidates of 3'-azido-3'-deoxithymidine (formulas II and III) which inhibit a human immunodeficient virus and having the following formulas I, II and III.



(12) МЕЖДУНАРОДНАЯ ЗАЯВКА, ОПУБЛИКОВАННАЯ В СООТВЕТСТВИИ С
ДОГОВОРом О ПАТЕНТНОЙ КООПЕРАЦИИ (РСТ)

(19) ВСЕМИРНАЯ ОРГАНИЗАЦИЯ
ИНТЕЛЛЕКТУАЛЬНОЙ СОБСТВЕННОСТИ
Международное бюро



(43) Дата международной публикации:
29 декабря 2004 (29.12.2004)

PCT

(10) Номер международной публикации:
WO 2004/113360 A1

(51) Международная патентная классификация:
C07H 19/10, A61P 31/18

(21) Номер международной заявки: PCT/RU2003/000514

(22) Дата международной подачи:
21 ноября 2003 (21.11.2003)

(25) Язык подачи: русский

(26) Язык публикации: русский

(30) Данные о приоритете:
2903119415 26 июня 2003 (26.06.2003) RU

(71) Заявители (для всех указанных государств, кроме
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(72) Изобретатели: и

(75) Изобретатели/заявители (только для (US)): ПОК-
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(81) Указанные государства (национально): CA, IN, JP,
US.

(84) Указанные государства (регионально): европеев-
ский патент (AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL,
PL, PT, RO, SE, SI, SK, TR).

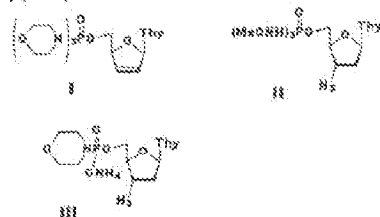
Опубликована

С отчётом о международной практике.

В антибиотик двухфазных кодов, кодов языков и дру-
гих сокращений см. «Пояснения и коды к сокращениям»,
публикуемые в начале каждого очередного выпуска бюл-
летеня PCT.

(54) Title: PHOSPHOROMIDATES OF NUCLEOSIDE ANALOGUES-REPRODUCTION INHIBITORS FOR HUMAN
IMMUNODEFICIENT VIRUS

(54) Название изобретения: ФОСФОРАМИДАТЫ НУКЛЕОЗИДНЫХ АНАЛОГОВ – ИНГИБИТОРЫ РЕПРО-
ДУКЦИИ ЧЕЛОВЕКА



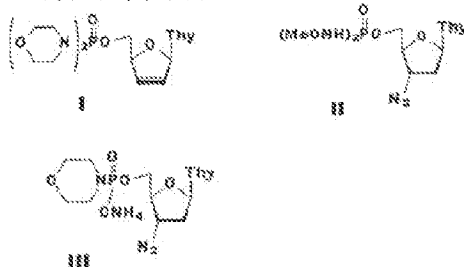
(57) Abstract: The invention relates to novel biologically active derivatives of 5'-phosphate 3'-azido-2',3'-dideoxythymidine and of 2',3'-dideoxy-2',3'-dihydrothymidine and can be used in the form of antiviral agents, first and foremost against a human immunodeficient virus (HIV). Said invention makes it possible to develop and use novel compounds which are resistant with respect to the action of dephosphorylation enzymes, capable to penetrate inside a cell and exhibit selective activity for suppressing DNA biosynthesis which is catalysed by the HIV reverse transcriptase. Said technical result is achieved by the novel inventive compounds, i.e. phosphoramidates of nucleoside analogues comprising 5'-phosphorimidate of 2',3'-dideoxy-2',3'-dihydrothymidine (formula I) and phosphoramidates of 3'-azido-2',3'-dideoxythymidine (formulas II and III) which inhibit a human immunodeficient virus and having the following formulas I, II and III.

[Продолжение на след. странице]

WO 2004/113360 A1



(57) Реферат: Изобретение относится к новым биологически активным производным 5'-фосфата 3'-азидо-3'-дезокситимидина и 2',3'-дидезоксикс-2',3'-дидегидротимидина и может быть использовано в качестве противовирусных средств, в первую очередь против вируса иммунодефицита человека (ВИЧ). Техническим результатом настоящего изобретения является создание и использование новых соединений, которые устойчивы к действию ферментов дефосфорилирования, способны проникать внутрь клетки и обладают избирательной активностью в подавлении биосинтеза ДНК, катализируемого обратной транскриптазой ВИЧ. Указанный технический результат достигается тем, что согласно изобретению, являются новые соединения: фосфорамидаты нуклеозидных аналогов, включающие 5'-фосфодиморфилат 2',3'-дидезоксикс-2',3'-дидегидротимидина (формула I) и фосфорамидаты 3'-азидо-3'-дезокситимидина (формулы II и III), ингибирующие активность репродукции вируса иммунодефицита человека и имеющие следующие формулы:



**Фосфорамидаты нуклеозидных аналогов -
ингибиторы репродукции вируса иммунодефицита человека**

Изобретение относится к новым биологически активным производным
5 5'-фосфата 3'-азидо-3'-дезокситимидина и 2',3'-дидезокси-2',3'-
дидегидротимидина и может быть использовано в качестве противовирусных
средств, в первую очередь против вируса иммунодефицита человека (ВИЧ).

Известно, что ингибировать репродукцию вируса иммунодефицита
можно на разных стадиях его жизненного цикла, но очевидно, что
10 целесообразно использовать ингибиторы наиболее ранних процессов.
Именно поэтому обратная транскриптаза ВИЧ, первый по времени
функционирования фермент в цикле репликации вируса, является наиболее
привлекательной мишенью для подавления размножения вируса.

В настоящее время известны различные соединения, подавляющие репродукцию
15 вируса иммунодефицита человека. Наиболее эффективными из известных соединений
являются 3'-азидо-3'-дезокситимидин (азидотимидин или AZT, зидовудин,
«Ретровир», «Тимазид»), находящий применение в медицинской практике (Mitsuya,
H.; Broder, S. Inhibition of the *in vitro* infectivity and cytopathic effect of human T-
lymphotropic virus type III/lymphadenopathy-associated virus/HTLV-III(LAV) by 2',3'-
20 dideoxynucleosides. *Proc. Nat. Acad. Sci. USA*, 1986, 83, 1911-1915), а также 2',3'-
дидезоксицитидин (ddC, зальцитабин, «Гивид»), 2',3'-дидезоксиинозин (ddI,
диданозин, «Видекс»), 3'-дезокси-2',3'-дидегидротимидин (d4T, ставудин,
«Зерит») и 3'-тиоцитидин (ЗТС, ламивудин, «Эпивир»).

Молекулярный механизм действия указанного соединения включает диффузию его
25 внутрь клетки, инфицированной ВИЧ. Далее он подвергается трифосфорилированию и
специфично блокирует синтез ДНК, катализируемый обратной транскриптазой ВИЧ.
Аналогичным образом действуют другие противовирусные нуклеозиды, применяемые в
медицинской практике для лечения СПИД: 2',3'-дидезоксицитидин и, 2',3'-
дидезоксиинозин (Mitsuya, H.; Broder, S. Inhibition of the *in vitro* infectivity and cytopathic
30 effect of human T-lymphotropic virus type III/lymphadenopathy-associated virus (HTLV-
III/LAV) by 2',3'-dideoxynucleosides. *Proc. Nat. Acad. Sci. USA*, 1986, 83, 1911-1915), 2',3'-

дидезокси-2',3'-дидегидротимидин (Herdewijn, P.; Balzarini, J.; DeClercq, E.; et al., 3'-Substituted 2',3'-dideoxynucleoside analogues as potential anti-HIV (HTLV/LAV) agents. *J. Med. Chem.*, 1987, 30, 1270-1278) и 2',3'-дидезокси-3'-тиотимидин (Soudeyns, H.; Yao, Q.; et al., Anti-human immunodeficiency virus type 1 activity and in vitro toxicity of 2'-deoxy-3'-thiacytidine (BCH-189), a novel heterocyclic nucleoside agents. *Antimicrob. Agents Chemother.*, 1991, 35, 1386-1390).

Однако, фосфорилирование модифицированных нуклеозидов клеточными ферментами происходит значительно менее эффективно, чем природных нуклеозидов. Процесс превращения нуклеозида в организме человека в соответствующий 5'-трифосфат занимает около 1,5-2 часов. За это время проникший в клетки вирус успевает в форме провирусной ДНК интегрировать в геном человека. Использование в качестве лекарственных препаратов нуклеозид-5'-трифосфатов с немодифицированной трифосфат-ной частью невозможно из-за их низкой стабильности к действию ферментов гидролиза и вследствие этого низкой способности проникать внутрь клетки. Таким образом, применяемые препараты, даже если они приняты в момент инфицирования, не могут предохранить от заражения ВИЧ.

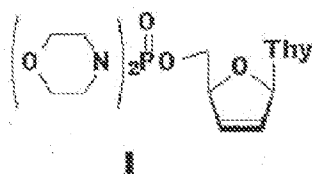
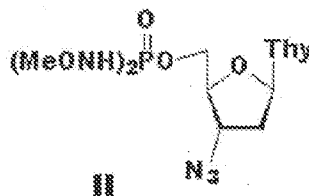
Наиболее близким техническим решением (прототипом) является использование в качестве противовирусного препарата производных 3'-азидо-3'-дидезокситимидина, содержащих модифицированную фосфатную группу в 5'-положении, а именно Н-фосфонат AZT (Патент США №5043437, МПК С 07 Н 19/00, опубл. 27.08.1991), а также: Н.Б.Тарусова, А.А.Хорлин, А.А.Краевский, и др., Ингибирование вируса иммунодефицита человека в культуре клеток 5'-фосфонатами 3'-азидо-2',3'-дидезоксинуклеозидов, *Мол. Биол.*, 1989, 23, №6, 1716-1724). В настоящее время он используется в качестве лекарственного средства под названием «Никавир» для лечения СПИД (ВИЧ-инфекций).

Однако, было показано, что в организме это соединение в основном подвергается дефосфорилированию, превращаясь в AZT (Кузнецова Е.В., Куханова М.К., и др. Реакция 5'-Н-фосфонатов, 5'-фторфосфатов и 5'-фосфатов модифицированных тимидинов в плазме крови.- *Мол. Биол.*, 1995, 29, N2, 415-420).

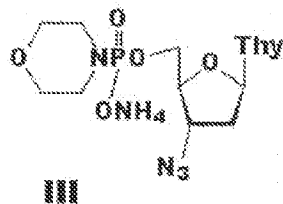
Техническим результатом настоящего изобретения является создание и использование новых соединений, которые устойчивы к действию ферментов дефосфорилирования, способны проникать внутрь клетки и обладают избирательной активностью в подавлении биосинтеза ДНК, катализируемого обратной транскриптазой ВИЧ.

Указанный технический результат достигается тем, что согласно изобретению, заявляются новые соединения: фосфорамидаты нуклеозидных аналогов, включающие 5'-фосфодиморфолидат 2',3'-дидезокси-2',3'-дидегидротимидина (формула I) и фосфорамидаты 3'-азидо-3'-дезокситимидина (формулы II и III), ингибирующие активность репродукции вируса иммунодефицита человека и имеющие следующие формулы:

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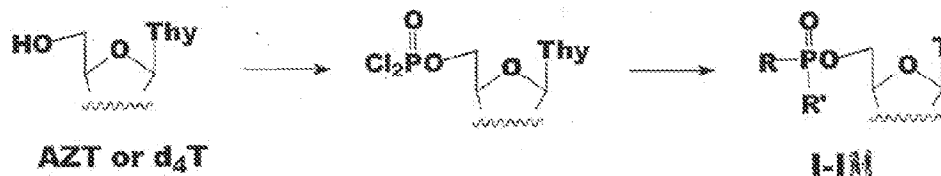


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Для получения соединений формул I-III был использован единый синтетический подход, заключающийся в реакции нуклеозида с хлорокисью фосфора в триэтилфосфате, с последующей обработкой полученного фосфодихлорида различными аминами. Полученные фосфорамидаты I-III могут быть выделены и очищены стандартными способами, например, экстракцией, осаждением, хроматографией и т.д.



Изобретение иллюстрируется следующими графическими материалами. На фиг. 1 приведены сравнительные графики анти-ВИЧ действия соединения формулы I в отношении ВИЧ-1 ГКВ 4046 при одновременном внесении с вирусом. На Фиг. 2 приведены сравнительные графики анти-ВИЧ действия соединения формулы I при внесении его после адсорбции вируса. На фиг. 3 – то же, анти-ВИЧ действие соединения формулы II при одновременном с вирусом внесении. На фиг. 4 – то же, анти-ВИЧ действие соединения формулы III при одновременном внесении с вирусом.

Настоящее изобретение обосновывается нижеследующими примерами получения данных соединений и результатами биохимических испытаний.

Пример 1. Получение 5'-фосфодиморфолата 2',3'-Дидезокси-2',3'-дидегидротимидин 5'-фосфодиморфолата (формула I)

К раствору 2',3'-дидезокси-2',3'-дидегидротимидина (235 мг, 1.05 ммоль) в триэтилфосфате (3 мл), при rt, при встряхивании, прибавили *tert*-бутанол (8.5 мг, 0.12 ммоль) и хлорокись фосфора (0.35 г, 2.24 ммоль). Реакционную смесь выдержали 16ч при rt, охладили до 4°C, после чего прибавили раствор морфолина (1.3 г, 15 ммоль) в метаноле (5 мл). Затем реакционную смесь (суспензию) разбавили этилацетатом (10 мл) и выдержали 18ч при 4°C. Выпавший осадок (хлорида морфолина) отфильтровали, маточник упарили и остаток разделяли колоночной хроматографией на силикагеле (10 г Silasorb в хлороформе), элюируя градиентом (0-5%) метанола в хлороформе. Выход титруемого соединения 0.87 ммоль (82%, по УФ), продукт содержал около 2 моль триэтилфосфата на моль диморфолата. Для повторной очистки была взята половина этого

количества. Очистку проводили на силикагеле (5 г Silasorb в хлороформе), элюируя 3% метанолом в хлороформе. Было получено 117 мг целевого соединения (0.264 ммоль, 50%).

^1H -ЯМР (D_2O): 7.49с (1H, H-6); 6.93 уш.с. (1H, H-1'); 6.54д. ($J=6.2$ Hz, 1H, H-3'); 6.10д ($J=6.2$ Hz, 1H, H-2'); 5.18 уш.с. (1H, H-4'); 4.22 и 4.07 2м (2H, H-5'); 3.67м (4H, CH_2O -морфолина); 3.13м (4H, CH_2N -морфолина); 1.94с (3H, Me тимина).

^{31}P -ЯМР (D_2O): 16.38с.

Пример 2. Получение 3'-Азидо-2',3'-дидезокситимидин 5'-фосфонс
(метоксиамида) (формула II)

К раствору 3'-азидо-3'-дезокситимидина (82 мг, 0.31 ммоль) в триэтилфосфате (1.7 г) при перемешивании, при rt, прибавили *трет*-бутанол (5 мг, 0.06 ммоль) и хлорокись фосфора (86 мг, 0.56 ммоль). Реакционную смесь выдержали 1ч при rt, а затем 20ч при 4°C, после чего к охлажденному раствору прибавили метоксиамид хлорогидрат (309 мг, 3.7 ммоль) и триэтиламин (0.51 г, 5.05 ммоль) в метаноле (5 мл). Выпавший осадок отфильтровали, маточник упарили и разбавили этилацетатом (10 мл). Вновь отфильтровали осадок, упарили маточник и выделяли продукт аналогично ранее описанному. Выход целевого соединения — 58 мг (0.143 ммоль, 46%)

^1H -ЯМР (D_2O): 7.49с (1H, H-6); 6.19т ($J=6.4$ Гц, 1H, H-1'); 4.49к ($J=6.7$ Гц, 1H, H-3'); 4.28-4.15м (3H, 2H-5'+H-4'); 3.62 д ($J=17$ Гц, 6H, 2 CH_2ON); 2.43т ($J=6.7$ Гц, 2H, 2H-2'); 1.86с (3H, Me тимина).

^{31}P -ЯМР (D_2O): 18.73с.

Пример 3. Получение 3'-Азидо-2',3'-дидезокситимидин
5'-фосфоморфолидат (формула III)

К раствору 3'-азидо-3'-дезокситимидина (178 мг, 0.67 ммоль) в триэтилфосфате (2.6 г) при перемешивании, при rt, прибавили *трет*-бутанол (7 мг, 0.09 ммоль) и хлорокись фосфора (170 мг, 1.09 ммоль). Реакционную смесь выдержали 1ч при rt, а затем 20ч при 4°C, после чего к охлажденному раствору прибавили воду (55 мг, 3.06 ммоль), выдержали 40 мин при 4°C,

прибавили морфолин (0.33 г, 3.8 ммоль) в метаноле (3 мл). Реакционную смесь упарили и разбавили этилацетатом (10 мл). Отфильтровали осадок, упарили маточник и выделяли продукт аналогично ранее описанному, используя для элюции систему хлороформ-метанол-25% водный аммиак (60:35:5). Выход целевого соединения – 182 мг (0.420 ммоль, 63%)

^1H -ЯМР (D_2O): 7.49с (1H, H-6); 6.16т (J=6.4 Гц, 1H, H-1'); 4.48к (J=6.7 Гц, 1H, H-3'); 4.25-4.14м (3H, 2H-5'+H-4'); 3.72м (2H, CH_2O -морфолина); 3.01м (2H, CH_2N -морфолина); 2.31т (J=6.7 Гц, 2H, 2H-2'); 1.88с (3H, Me тимина).

^{31}P -ЯМР (D_2O): 7.81с.

Далее приведены исследования ингибирования репродукции ВИЧ.

Исследование ингибирования репродукции ВИЧ включает культивирование первично инфицированных лимфоидных клеток линии MT-4 в присутствии исследуемых соединений, конечные концентрации которых в культуральной среде составляют 0,0001-100 мкг/мл, на протяжении одного пассажа - в течение 4 суток.

Об ингибировании репродукции ВИЧ в культуре чувствительных клеток судят по снижению накопления вирусспецифического белка p24 (по данным иммуноферментного анализа), а так же по увеличению жизнеспособности клеток в присутствии препарата по сравнению с контролем, определяемому на 4-е сутки культивирования при окрашивании 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT).

Пример 4. Оценка цитотоксичности заявляемых соединений

Цитотоксичность препарата оценивают путем добавления его разведений в бессывороточной среде RPMI-1640 к клеточной суспензии MT-4, помещенной в лунки 96-луночного планшета ("Orange"), до конечных концентраций 0,001-100 мкг/мл (по три лунки на каждую дозу) с последующим культивированием при 37°C в течение 4 суток. Посевная концентрация составляет $0,5 \times 10^6$ клеточных частиц в миллилитре. Контролем служат клетки без добавления препарата, вместо которого вносят такое же

количество бессывороточной среды. Жизнеспособность клеток подсчитывают на 4 сутки культивирования, пользуясь формазановым методом (прижизненным окрашиванием клеток 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) [Leslie R.Bisset, Hans Lutz, Jurg Boni, Regina Hoffmann-Lehmann, Ruedi Luthy, Jorg Schupbach. Combined effect of zidovudine (ZDV), lamivudine (3TC) and abacavir (ABC) antiretroviral therapy in suppressing in vitro FIV replication. *Antiviral Research* 53 (2002) 35-45].

Токсичность различных доз препарата определяют по жизнеспособности клеток относительно контроля, по полученным результатам строят дозозависимую кривую и определяют концентрацию, на 50% снижающую жизнеспособность клеток (CD_{50}). Следует отметить, что исследуемые соединения не оказывают токсического действия на клетки MT-4 в эффективных концентрациях: 50% токсичные дозы на 5-6 порядков превышают эффективные в отношении ВИЧ-1 дозы (таблица).

15

Таблица

Количественные характеристики анти-ВИЧ действия соединений

Соединение	CD_{50} , М	Одновременное внесение			Добавление после адсорбции вируса		
		ID_{50} PD_{50}	ID_{50}	IS	ID_{50} PD_{50}	ID_{50}	IS
d4T	314,0	0,01 2,4	0,3	31400	0,24 23,8	23,8	1308,3
I (IMB-43)	>226	<0,0022 0,0022	<0,002 2	>102727	<0,0022 0,22	16,9	>10272 7
AZT	37,4	0,037 18,7	1,87	1010	0,0037 18,7	0,09	10100
II (IMB-94)	740,2	0,012 0,37	0,2	61683	0,025	0,22	29608
III (IMB-101)	>230,7 6	0,023 -	1,0	10033	0,07 -	0,2	3296,6

20

Пример 5. Изучение влияния заявляемых соединений на репродукцию ВИЧ-1 в культуре клеток MT-4.

Исследование противовирусной активности соединений в отношении ВИЧ-1 проводят на перевиваемой линии чувствительных клеток MT-4. Для

заражения используют супернатант инфицированных клеток, хранящийся в жидком азоте, множественность заражения составляет 0,2-0,5 инфекционных единиц на клетку. Суспензию клеток MT-4 с концентрацией $2,0 \times 10^6$ клеточных частиц в миллилитре и жизнеспособностью не менее 90% помещают в лунки 96-луночного планшета непосредственно после внесения вирусодержащего материала и сразу же добавляют исследуемые соединения, разведенные в среде RPMI-1640 без сыворотки, до конечных концентраций 0,0001-100 мкг/мл (по три лунки на каждую дозу). Контролями служат инфицированные ВИЧ-1 клетки MT-4 без добавления препарата (вместо препарата вносят такое же количество среды RPMI-1640 без добавок) и неинфицированные клетки.

Планшет инкубируют в течение часа при 37°C для адсорбции вируса, затем клетки разводят до посевной концентрации ($0,5 \times 10^6$ в миллилитре) питательной средой RPMI-1640 с добавлением 10% фетальной сыворотки КРС, предварительно инактивированной прогреванием при 56°C в течение 30 минут, 300мг/мл L-глутамина и 100 мкг/мл гентамицина. Затем планшет помещают в термостат на 37°C в атмосфере 5% CO₂. На 4 сутки культивирования подсчитывают концентрацию и жизнеспособность клеток формазановым методом. По полученным данным строят графики зависимости прироста жизнеспособности клеток относительно контроля под действием возрастающих доз препаратов, т.е. определяют способность препаратов защищать инфицированные клетки от цитопатогенного действия вируса. Оценку анти-ВИЧ активности соединений проводят с использованием количественного определения вирусспецифического белка p24 методом прямого иммуноферментного анализа, как описано в [Leslie R.Bisset, Hans Lutz, Jurg Boni, Regina Hoffmann-Lehmann, Ruedi Luthy, Jorg Schupbach. Combined effect of zidovudine (ZDV), lamivudine (3TC) and abacavir (ABC) antiretroviral therapy in suppressing in vitro HIV replication. *Antiviral Research* 53 (2002) 35-451], и строят дозозависимые кривые (фиг.1-4), по которым рассчитывают концентрации, на 50 и 90% подавляющие прирост

вирусного антигена (ID_{50} и ID_{90}). Терапевтический индекс, или индекс селективности (IS) считают как отношение 50%-ной токсической концентрации соединения к его 50%-ной эффективной дозе. Соединение I (2',3'-Дидезокси-2',3'-дидегидротимидин 5'-фосфодиморфолидат) при
5 внесении в культуру чувствительных клеток одновременно с ВИЧ по своей эффективности на порядок и более превосходит исходный препарат d4T по ID_{50} и на два порядка по ID_{90} , при внесении после адсорбции вируса - на два порядка превосходит исходный препарат по ID_{50} при почти одинаковом уровне 90%-го ингибирования. Соединения II (3'-Азидо-2',3'-
10 дидезокситимидин 5'-фосфобис (метоксиамид)) и III (3'-Азидо-2',3'-дидезокситимидин 5'-фосфоморфолидат) проявили активность, сравнимую с активностью исходного азидотимидина, примерно одинаковую при добавлении одновременно с ВИЧ и при добавлении в постадсорбционных условиях. На основании этих количественных показателей ингибирования
15 можно судить об эффективности противовирусного действия новых соединений, заключающейся в высокой степени подавления репликации ВИЧ-1 в культуре клеток MT-4 и превышающей эффективность исходных d4T и AZT.

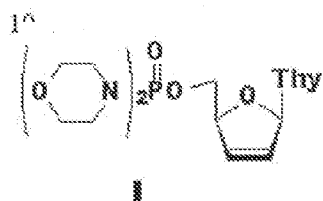
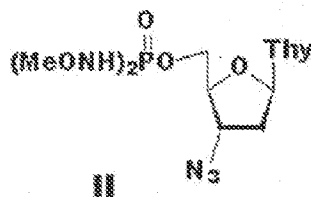
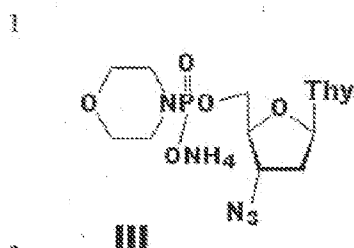
20

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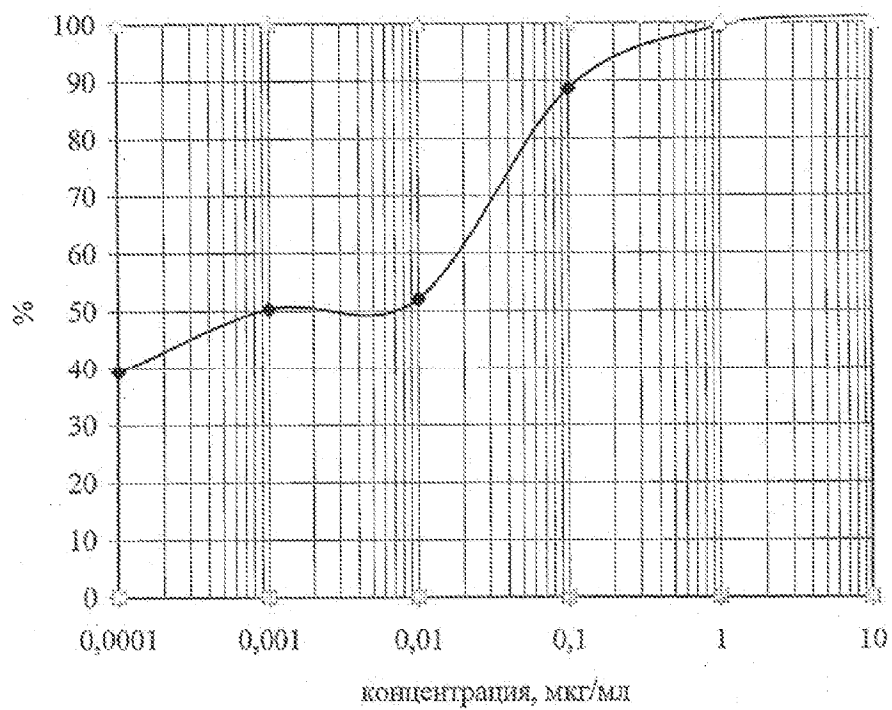
30

Формула изобретения

Фосфорамидаты нуклеозидных аналогов, включающие 5'-
5. фосфодиморфолонат 2',3'-дидезокси-2',3'-дигидротимидина (формула I) и
фосфорамидаты 3'-азидо-3'-дезокситимидина (формулы II и III),
ингибирующие активность репродукции вируса иммунодефицита человека и
имеющие следующие формулы:



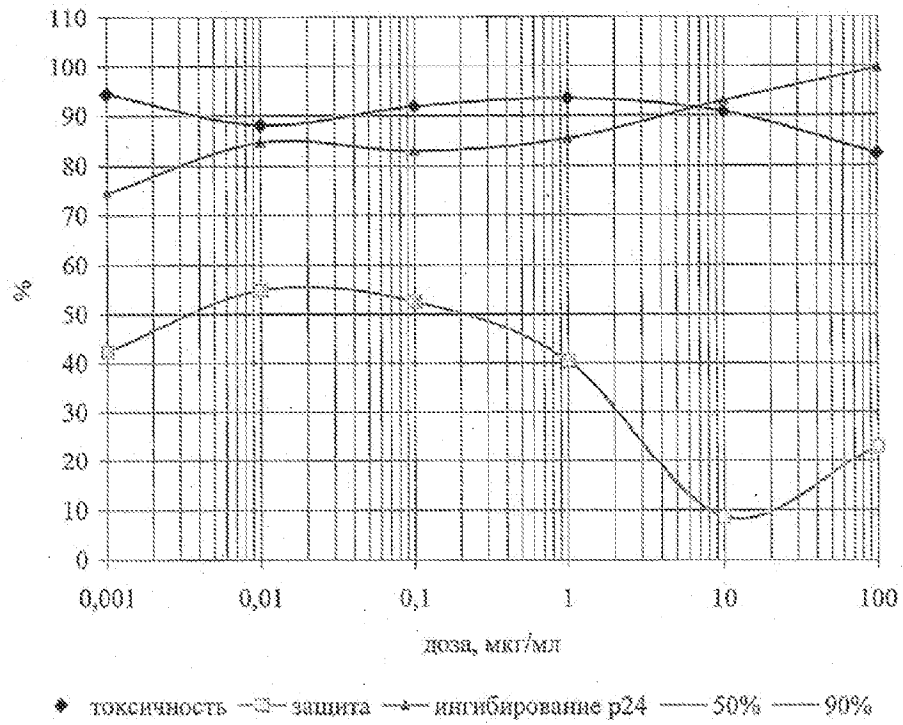
1/4



♦ ингибитор —■— защита —▲— токсичен

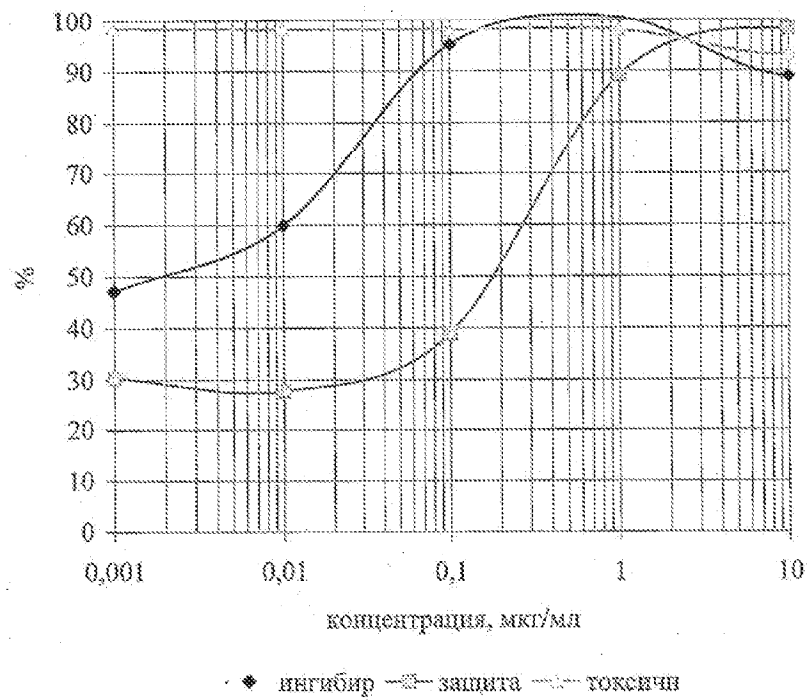
Фиг. 1

2/4



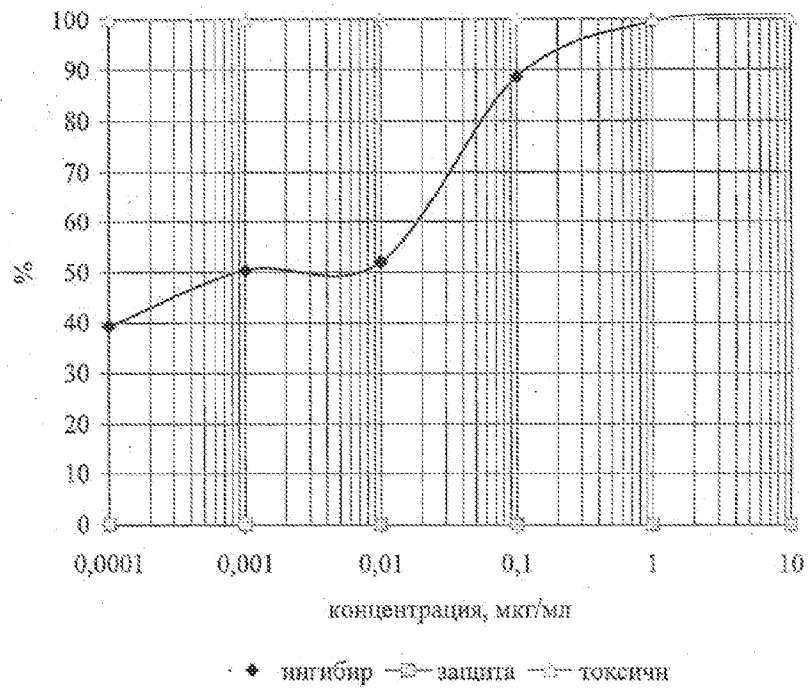
Фиг.2

3/4



Фиг.3

4/4



Фиг.4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/RU 2003/000514

A. CLASSIFICATION OF SUBJECT MATTER		
C07H 19/10, A61P 31/18		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
C07H 19/10, 19/06, 19/073, A61R 31/7072, A61P 31/18		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	SHIPITSYN A.V. et al. Phosphorodiamides as prodrugs for antiviral nucleosides, Nucleosides, Nucleotides & Nucleic acids, 2003, v. 22, № 5-8, p. 963-966. (soedineniya Ib, Iia, IIIa, page 964)	1
A	RU 2006123650/04 A (ZAKRYTOE AKTSIONERNOE OBSHCHESTVO "PROIZVODSTVENNO-KOMMERCHESKAYA ASSOTSIATSIYA AZT"), 27.08.2002, BI № 24, pages 132-133, the claims	1
A	US 5233031 A (UNIVERSITY OF ROCHESTER) 03.08.1993	1
A	US 6455513 B1 (UNIVERSITY COLLEGE CARDIFF CONSULTANTS Ltd. et al.) 24.09.2002	1
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search (08.04.2004)		Date of mailing of the international search report (22.04.2004)
Name and mailing address of the ISA/ RU		Authorized officer
Facsimile No.		Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

ОТЧЕТ О МЕЖДУНАРОДНОМ ПОИСКЕ

Международная заявка №
PCT/RU 2003/000514

А. КЛАССИФИКАЦИЯ ПРЕДМЕТА ИЗОБРЕТЕНИЯ:		
C07H 19/10, A61P 31/18		
Согласно международной патентной классификации (МПК-7)		
В. ОБЛАСТИ ПОИСКА:		
Проверенный минимум документации (система классификация и индексы) МПК-7:		
C07H 19/10, 19/06, 19/073, A61P 31/7072, A61P 31/18		
Другая проверенная документация в той мере, в какой она включена в поисковые подборки:		
Электронная база данных, использованная при поиске (название базы и, если возможно, поисковые термины):		
С. ДОКУМЕНТЫ, СЧИТАЮЩИЕСЯ РЕЛЕВАНТНЫМИ:		
Категория*	Ссылки на документы с указанием, где это возможно, релевантных частей	Относится к пункту №
P, X	SHIPITSYN A.V. et al. Phosphorodiamides as prodrugs for antiviral nucleosides, Nucleosides, Nucleotides & Nucleic acids, 2003, v. 22, № 5-6, p. 963-966 (соединения Ib, IIa, IIIa, с. 964)	1
A	RU 2000123650/04 А (ЗАКРЫТОЕ АКЦИОНЕРНОЕ ОБЩЕСТВО "ПРОИЗВОДСТВЕННО-КОММЕРЧЕСКАЯ АССОЦИАЦИЯ АЗТ") 27.08.2002, БИ №24, с. 132-133, формула	1
A	US 5233631 A (UNIVERSITY OF ROCHESTER) 03.08.1993	1
A	US 6455513 B1 (UNIVERSITY COLLEGE CARDIFF CONSULTANTS Ltd. et al.) 24.09.2002	1
☐ Исследованные документы указаны в продолжении графы С. ☐ Данные о патентах-аналогах указаны в приложении		
* Ссылки категории относятся к документам: А документ, определяющий общий уровень техники В более ранний документ, не опубликованный на дату международной подачи или после нее С документ, относящийся к уровню раскрытия, экспозиции, раскрытия и т.д. Р документ, опубликованный до даты международной подачи, но после даты направления заявки на приоритет и т.д. Т более поздний документ, опубликованный после даты приоритета и присвоенный для признания изобретения X документ, имеющий наиболее близкое отношение к предмету поиска, порочащий новизну и изобретательский уровень Y документ, порочащий изобретательский уровень в сочетании с одним или несколькими документами той же категории Z документ, являющийся патентом-аналогом		
Дата действительного завершения международного поиска: 08 апреля 2004 (08.04.2004)		Дата отправки настоящего отчета о международном поиске: 22 апреля 2004 (22.04.2004)
Наименование и адрес Международного поискового органа: Федеральный институт промышленной собственности РФ, 123995, Москва, Г-59, ГСП-5, Борокская наб., 30.1. Факс: 243-3337, телетайп: 114818 ПОДАЧА		Уполномоченное лицо: Е. Лубако Телефон № 240-25-91

Форма PCT/ISA/210 (второй лист)(июль 1998)

Electronic Acknowledgement Receipt	
EFS ID:	46173449
Application Number:	17077267
International Application Number:	
Confirmation Number:	4237
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	117796
Filer:	Joy Lynn Bala Nemirow/Joannah Laluces
Filer Authorized By:	Joy Lynn Bala Nemirow
Attorney Docket Number:	37JD-199059-US13
Receipt Date:	12-JUL-2022
Filing Date:	22-OCT-2020
Time Stamp:	19:35:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$260
RAM confirmation Number	E20227BJ40082532
Deposit Account	504561
Authorized User	Joannah Laluces
<p>The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:</p> <p>37 CFR 1.16 (National application filing, search, and examination fees)</p> <p>37 CFR 1.17 (Patent application and reexamination processing fees)</p>	

37 CFR 1.19 (Document supply fees)					
37 CFR 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Amendment/Request for Reconsideration-After Non-Final Rejection	37JD-199059-US13_Amendment_and_Reply_to_NonFinal_Office_Action.pdf	216695	no	11
			29a080cd33bd40545d83719991a0e272337f847a		
Warnings:					
Information:					
2	Transmittal Letter	37JD-199059-US13_IDS_Transmittal_Letter.pdf	95245	no	2
			a753fcbf24c41330f91c8e542fbbba87d1b6508a7		
Warnings:					
Information:					
3	Information Disclosure Statement (IDS) Form (SB08)	37JD-199059-US13_IDS_SB08.pdf	125269	no	1
			08ef510961dff4be276f946a15270b4dfd4d2d37		
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
4	Foreign Reference	WO2004113360.pdf	2851704	no	20
			4c2a097a3d28b6da1ddcd77f17fbdccabf1a87d0		
Warnings:					
Information:					
5	Non Patent Literature	BlanverThirdPartyOpinion_BRPI08096546_2020-12-18.pdf	579591	no	26
			71f5b0c5207d595ae13c232cd01954ec0fb30d50		
Warnings:					
Information:					
6	Non Patent Literature	OfficeActionandSearchReport_CN2018112805090_2022-03-03.pdf	1954047	no	22
			287e3abed1a4cffeaaed7cba38dcbcd9cb01df1d8		
Warnings:					

Information:					
7	Non Patent Literature	Erti1995.pdf	727226	no	9
			d48d4ffe52ae4c042f8dd87ade5c96e5ee7e15fb		
Warnings:					
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8	Non Patent Literature	OfficeAction_CN201811280064_6_2022-04-02.pdf	1126114	no	13
			2d26e8867dbcd9904cab9fcb7fc3b1edcfdca08d		
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9	Non Patent Literature	OfficeAction_CN201811348434_5_2022-04-02.pdf	1102927	no	12
			0e414f9b5f8a397212e95f1ec11fd2db97e217c3		
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10	Non Patent Literature	OfficialAction_AR20170103608_2022-01-26.pdf	328314	no	6
			11788c1bda4f9e296665782e9a1d530804aec461		
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11	Non Patent Literature	OfficialAction_RU2018103329_2021-05-24.pdf	666825	no	26
			6dc94098bc5b8b907043bef446b168b1f29aaab6		
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12	Non Patent Literature	OppositionbyYLMurthy.pdf	475048	no	17
			8cf75cb2f07d66c57a14cb40017b7614ebc8312		
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Information:					
13	Non Patent Literature	RejectResolution_AR20120100340_2022-05-31.pdf	395249	no	16
			d681b79d6326a2e406b0965be5089ccd30b39572		
Warnings:					
Information:					

14	Fee Worksheet (SB06)	fee-info.pdf	38168	no	2
			cc0aa30427c3eea4f27eb40926c1b7ab0d5b7eda		
Warnings:					
Information:					
Total Files Size (in bytes):			10682422		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gilead Pharmasset LLC

Application No.: 17/077,267

Confirmation No.: 4237

Filed: October 22, 2020

Art Unit: 1623

For: NUCLEOSIDE PHOSPHORAMIDATE
PRODRUGS

Examiner: Patrick T. Lewis

AMENDMENT AND REPLY TO NON-FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.111

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This Amendment and Reply is responsive to the Non-Final Office Action dated April 12, 2022, concerning the above-referenced patent application. The Office set forth a three-month period to reply. Accordingly, this reply is timely filed on its due date of July 12, 2022. In response to the Action, please amend the above-identified U.S. patent application as follows:

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begin on page 3 of this paper.

Remarks/Arguments begin on page 7 of this paper.

AMENDMENTS TO THE SPECIFICATION

On page 1, under "CROSS REFERENCE TO RELATED APPLICATIONS", please amend the first paragraph as follows:

-- This application is a continuation of U.S. Patent Application No. 16/817,318, filed March 12, 2020, now abandoned, which is a continuation of U.S. Patent Application No. 16/516,192, filed July 18, 2019, now abandoned, which is a continuation of U.S. Patent Application No. 16/169,878, filed October 24, 2018, now abandoned, which is a continuation of U.S. Patent Application No. 15/411,506, filed January 20, 2017, now U.S. Patent No. 10,183,037, which is a continuation of U.S. Patent Application No. 14/656,546, filed March 12, 2015, now U.S. Patent No. 9,585,906, which is a continuation of U.S. Patent Application No. 14/013,237, filed August 29, 2013, now U.S. Patent No. 9,085,573, which is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent No. 8,580,765, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent No. 8,334,270, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent No. 7,964,580, which claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application Nos. 60/909,315, filed March 30, 2007, and 60/982,309, filed October 24, 2007, all of which are hereby incorporated by reference in their entireties. --

REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the following remarks.

Amendments to the Specification

The first paragraph of the specification is amended to update the priority information to include the status for U.S. Patent Application No. 16/817,318. No new matter is added by virtue of this amendment; thus, entry thereof is respectfully requested.

Amendments to the Claims

By this paper, claims 17-19 are amended. Support for the amendments may be found, for example, on pages 671-672 of the specification as filed. The amendments do not introduce new matter, and thus Applicant respectfully requests their entry. Applicant reserves the right to pursue canceled subject matter in a continuing application.

Upon entry of this amendment, claims 13-19 are currently pending and under examination in this application.

Rejection under 35 U.S.C. § 112

Claims 17-19 are rejected under 35 U.S.C. § 112(d) or pre-AIA 35 U.S.C. § 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.

Without acquiescing to the propriety of the rejection, but in a sincere attempt to expedite prosecution, the claims have been amended, rendering the objection moot.

Rejection under 35 U.S.C. § 103

Claims 13-16 are rejected under pre-AIA 35 U.S.C. § 103(a) as allegedly being unpatentable over WO 2005/003147 A2 (hereinafter “Clark”) and Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (hereinafter “Perrone”) in combination.

The Office cites two purine-containing compounds of Clark (see Office Action at p. 5) and relies on Clark for allegedly “teach[ing] or reasonably suggest[ing] a nucleoside or monophosphate thereof corresponding to instant formula I-6” and “further reasonably suggest[ing] nucleotide prodrugs (protides) thereof.” Office Action at p. 6.

While the Office acknowledges that “Clark does not explicitly teach or exemplify a protide of a (2’R)-2’-deoxy-2’-fluoro-2’C-methyl nucleotide in a single embodiment,” the Office relies on Perrone for allegedly “teach[ing] or reasonably suggest[ing] a phosphoramidate moiety corresponding to instant compound I-6.” Office Action at p. 6 and 8. Thus, the Office alleges that “it would have [been] obvious to one of ordinary skill in the art at the time of invention to provide the anti-HCV compounds of Clark . . . as a protide/prodrug wherein the H of the 5’OH moiety is replaced by a phosphoramidate moiety of Perrone.” Office Action at p. 8.

Applicant traverses the rejection at least for the reasons set forth below.

Applicant respectfully submits that the Office has not established *prima facie* case of obviousness as the standard employed in the Office Action is incorrect. If the “lead compound analysis” required by Federal Circuit decisions is applied, a *prima facie* obviousness cannot be established. *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). As such, Applicants are “under no obligation to submit evidence of nonobviousness.” MPEP § 2142.

The Legal Standard for Determining Obviousness

The Office’s obviousness rejection is not supported by sufficient legal basis. Under the standard established by Federal Circuit case law, a lead compound analysis is required when determining obviousness for chemical compounds.

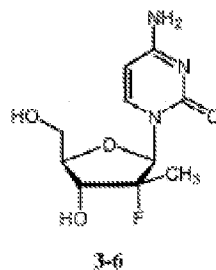
Lead Compound Analysis Required by the Federal Circuit in Determining Obviousness of Chemical Compounds

The lead compound analysis is a two-step analysis. First, “*prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.” *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). It requires a demonstration “that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art.” *Daiichi Sankyo Co. v. Matrix Laboratories Ltd.*, 96 USPQ2d 1526, 1533 (Fed. Cir. 2010). Second, after a lead compound has been identified, a determination is required as to whether “the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound.” *Eisai*, 533 F.3d at 1359.

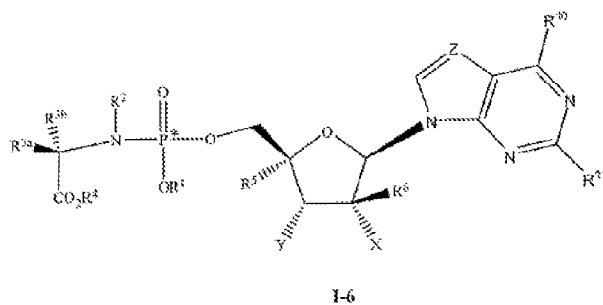
Applicants submit that the claimed compounds of formula I-6 are not obvious under the lead compound analysis.

Clark describes a genus covering several compounds. *See, e.g.*, page 17, line 3 to page 18, line 17. Clark further discloses several specific compounds, most of which have a different base than the claimed compounds of formula I-6.

The claimed compounds of formula I-6 are not obvious as Clark does not teach or suggest, and the Office has not stated any rational basis for a person skilled in the art to determine, what is or are the lead compound(s) out of the various compounds taught in Clark. Assuming *arguendo*, one of ordinary skill in the art would choose a compound out of Clark, one of ordinary skill would look to the biological data provided in Tables 1-9 in Example 5 of Clark and select (2'R)-2'-deoxy-2'fluoro-2'-C-methylcytidine (shown below) as a lead compound for further modification:



See, e.g. page 76-77 of Clark. Such a compound has a different base than the claimed compounds of formula I-6:



As such, even assuming *arguendo* one of ordinary skill would select a lead compound from Clark, such a compound would be structurally distinct from the claimed compounds of formula I-6. The Office's citation to two purine-containing compounds of Clark can only be based on impermissible hindsight.

Further, one of ordinary skill in the art would not be motivated to make the required modifications to arrive at the claimed compounds based on the disclosure of any of the cited art because there is no reasonable expectation of success.

Perrone fails to cure the deficiencies of Clark as Perrone's teachings are limited to protide approaches for 4'-azidouridine. Clarke and Perrone disclose different nucleosides (having different substitutions on the sugar ring and different bases). Perrone itself notes that "4'-azidocytidine was discovered as a potent inhibitor of HCV replication" but "the corresponding uridine analogue, 4'-azido-uridine . . . was inactive as an inhibitor." Perrone at p. 1840.

Accordingly, one of ordinary skill would understand that modification of even the base may lead to change in biological activity. As such, one of ordinary skill would not be motivated to look to the teachings of Perrone directed to compounds having uridine. Further, one of ordinary skill would not have a reasonable expectation of success of applying the protide approaches of Perrone to achieve compounds of formula I-6.

For at least the foregoing reasons, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-4561. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 50-4561.

Respectfully submitted,

Dated: July 12, 2022

By /Joy Lynn Nemirow/
Joy Lynn Nemirow, Ph.D.
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Attorney for Applicant
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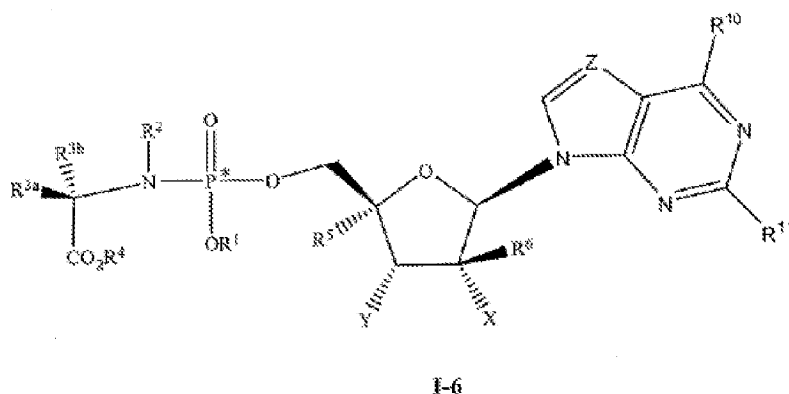
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-12. (Canceled)

13. (Previously presented) A compound of formula **I-6**:



wherein:

- (a) R^1 is H, -CH₃, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;
- (b) R^2 is H;
- (c) R^{3a} is H and R^{3b} is H, -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH₂Ph or lower cycloalkyl;
- (d) R^4 is hydrogen, -CH₃, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 2-butyl, *t*-butyl, benzyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl or di(C₁₋₆ alkyl)amino-C₁₋₆ alkyl;
- (e) R^5 is H;
- (f) R^6 is H, -CH₃, -CH₂F, -CHF₂, -CF₃ or -F;
- (g) X is H, -OH, -OCH₃, -F, -NH₂ or -N₃;

with the proviso that X cannot be OH when R^6 is -CH₃ or -CH₂F;

- (h) Y is -OH, -NH₂, -OCH₃ or -OC(O)CH₃;
- (i) R¹⁰ and R¹¹ are independently H, -F, -Br, -I, -OH, -OR', -NH₂, -NHR', -NR'₂, -CO₂R', -CONH₂, -CONHR', -CONR'₂, -CH=CHCO₂H or -CH=CHCO₂R', with the proviso that when R¹⁰ is -OH, R¹¹ is not -NH₂;
- (j) Z is N or -CR¹²;
wherein R¹² is H, halogen, -OR', -NH₂, -NHR', -NR'₂, -NO₂, C₁₋₆ alkyl, -CO₂R', -CONH₂, -CONHR', -CONR'₂, -CH=CHCO₂H or -CH=CHCO₂R';
- (k) R' is C₁₋₆ alkyl, a lower cycloalkyl or -C(O)(C₁₋₆ alkyl) or alternatively, in the instance of -NR'₂, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and
- (l) P* is a chiral phosphorus atom;
or a pharmaceutically acceptable salt thereof.

14. (Previously presented) The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

- (a) R¹ is phenyl;
- (b) R² is H;
- (c) R^{3a} is H and R^{3b} is -CH₃;
- (d) R⁴ is -CH₃, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, 2-butyl or *t*-butyl;
- (e) R⁵ is H;
- (f) R⁶ is -CH₃;
- (g) X is -F;
- (h) Y is -OH;
- (i) R¹⁰ is H, -NH₂, -NHR' or -NR'₂ and R¹¹ is H, -OH or -NH₂;
- (j) Z is N;
- (k) R' is C₁₋₆ alkyl or a lower cycloalkyl, or alternatively, in the instance of -NR'₂, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms; and
- (l) P* is a chiral phosphorus atom.

15. (Previously presented) The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein:

(a) R^{10} is $-NH_2$, $-NHR'$ or $-NR'^2$.

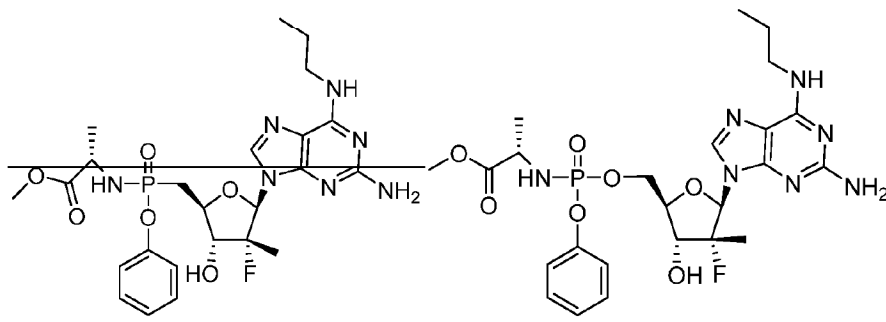
16. (Previously presented) The compound of claim 15, wherein:

(a) R^4 is $-CH_3$, ethyl, *n*-propyl or *i*-propyl;

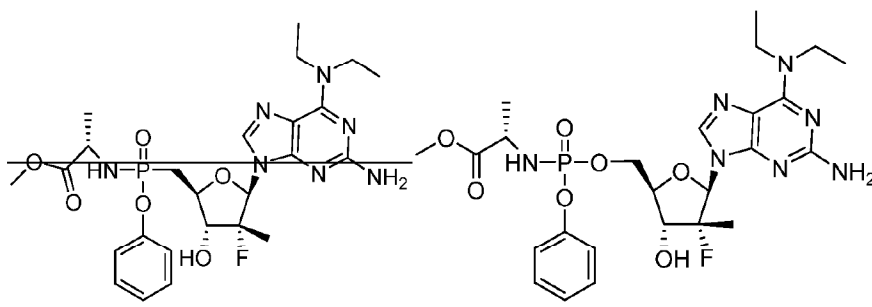
(b) R^{10} is $-NHR'$ and R^{11} is $-NH_2$; and

(c) R' is C_{1-6} alkyl.

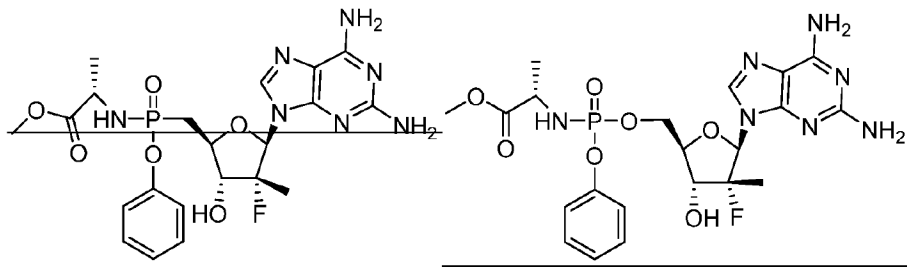
17. (Currently Amended) The compound of claim 16, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula:



18. (Currently Amended) The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula:



19. (Currently Amended) The compound of claim 14, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula:



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gilead Pharmasset LLC

Application No.: 17/077,267

Confirmation No.: 4237

Filed: October 22, 2020

Art Unit: 1623

For: NUCLEOSIDE PHOSPHORAMIDATE
PRODRUGS

Examiner: Patrick T. Lewis

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the "References Cited" on any patent to issue therefrom.

This Information Disclosure Statement is filed more than three months after the filing date of this application, OR more than three months after the date of entry of the national stage in the international application, AND after the mailing date of a first Office Action on the merits, but before the mailing date of any of a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311 or an action that otherwise closes prosecution in this application (37 C.F.R. § 1.97(c)).

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patent and non-patent literatures in accordance with 37 C.F.R. § 1.98(a)(2).

Not all documents are in English. English abstracts or equivalents are provided where available. Applicant is happy to provide English translations upon request. Applicant submits that the absence of an English translation does not relieve the PTO from its duty to consider the submitted foreign language document (37 C.F.R. § 1.98 and M.P.E.P. § 609).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50-4561 in the amount of \$260.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50-4561.

Respectfully submitted,

Dated: July 12, 2022

By /Joy Lynn Nemirow/
Joy Lynn Nemirow, Ph.D.
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Attorney for Applicant
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(650) 815-2634
Customer Number: 117796

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 17/077,267		Filing Date 10/22/2020		☐ To be Mailed					
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO													
APPLICATION AS FILED - PART I													
		(Column 1)		(Column 2)									
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A							
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A							
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *				x \$100 =							
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$480 =							
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).											
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))													
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL							
APPLICATION AS AMENDED - PART II													
AMENDMENT	07/12/2022	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR		(Column 3) PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)			
	Total (37 CFR 1.16(i))	* 7	Minus	** 20	= 0			x \$100 =		0			
	Independent (37 CFR 1.16(h))	* 1	Minus	*** 3	= 0			x \$480 =		0			
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE		0	
AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR		(Column 3) PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)			
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	Independent (37 CFR 1.16(h))	*	Minus	***	=			x \$0 =					
	☐ Application Size Fee (37 CFR 1.16(s))												
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))												
										TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.										LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".										/TINA J BARDEN/			
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".													
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.													

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

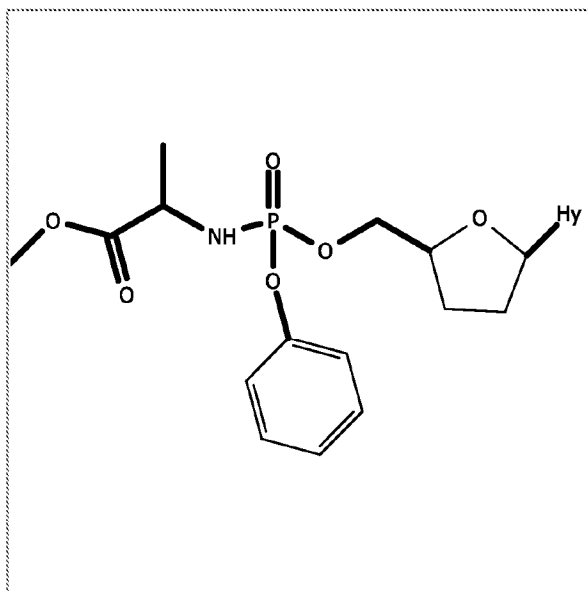
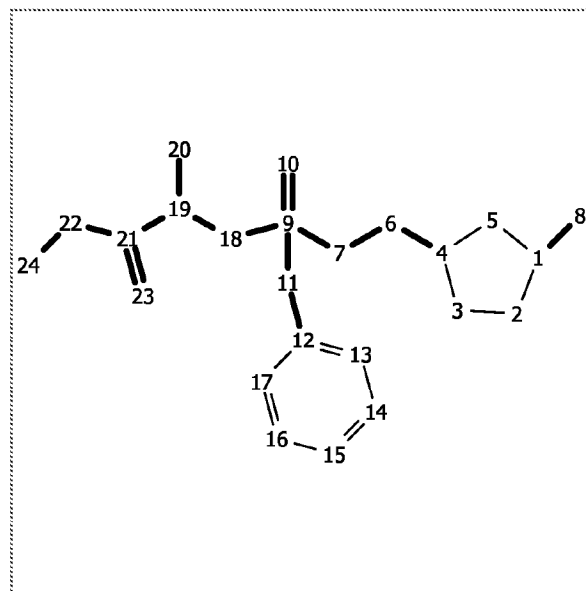
Structure Details

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 12, 13, 14, 15, 16, 17	Ring				
6, 7, 9, 10, 11, 19, 20, 21, 22, 23, 24	Chain				

Bond Attributes

Bond	Type	Value
12-13, 13-14, 14-15, 15-16, 16-17, 17-12	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
4-6, 19-21, 19-20	Chain	Exact
1-8, 6-7, 7-9, 9-18, 9-10, 9-11, 11-12, 18-19, 21-22, 21-23, 22-24	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17	Atom	Limited
6, 7, 9, 10, 11, 18, 19, 20, 21, 22, 23, 24	Class	Limited

FILE 'REGISTRY' ENTERED AT 19:00:17 ON 06 APR 2022
L1 STRUCTURE UPLOADED
L2 2 S L1 SSS SAM
L3 14 S L1 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 19:08:49 ON 06
APR 2022
L4 3 S L3

FILE 'REGISTRY' ENTERED AT 19:18:38 ON 06 APR 2022
L5 STRUCTURE UPLOADED
L6 50 S L5 SSS SAM
L7 2512 S L5 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 19:20:51 ON 06
APR 2022
L8 2541 S L7

FILE 'REGISTRY' ENTERED AT 19:21:07 ON 06 APR 2022
L9 STRUCTURE UPLOADED
L10 4 S L9 SSS SAM
L11 121 S L9 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 19:23:05 ON 06
APR 2022
L12 7 S L11



UNITED STATES PATENT AND TRADEMARK OFFICE

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 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 4237

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
17/077,267	10/22/2020	514	1623	37JD-199059-US13		
APPLICANTS GILEAD PHARMASSET LLC, FOSTER CITY, CA; INVENTORS Jinfa Du, Redwood City, CA; Dhanapalan Nagarathnam, Bethany, CT; Michael Joseph Sofia, Doylestown, PA; Peiyuan Wang, San Mateo, CA;						
** CONTINUING DATA ***** This application is a CON of 16/817,318 03/12/2020 ABN which is a CON of 16/516,192 07/18/2019 ABN which is a CON of 16/169,878 10/24/2018 ABN which is a CON of 15/411,506 01/20/2017 PAT 10183037 which is a CON of 14/656,546 03/12/2015 PAT 9585906 which is a CON of 14/013,237 08/29/2013 PAT 9085573 which is a CON of 13/609,614 09/11/2012 PAT 8580765 which is a CON of 13/099,671 05/03/2011 PAT 8334270 which is a CON of 12/053,015 03/21/2008 PAT 7964580 which claims benefit of 60/982,309 10/24/2007 and claims benefit of 60/909,315 03/30/2007						
** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 12/01/2020						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged <u>/PATRICK T LEWIS/</u> Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 0	TOTAL CLAIMS 7	INDEPENDENT CLAIMS 1
ADDRESS Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626 UNITED STATES						
TITLE NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS						
FILING FEE RECEIVED 6180	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)		

	☐ Other _____
	☐ Credit

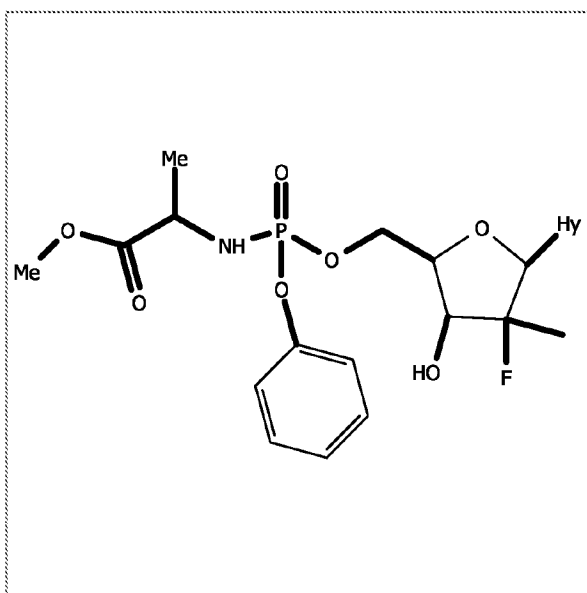
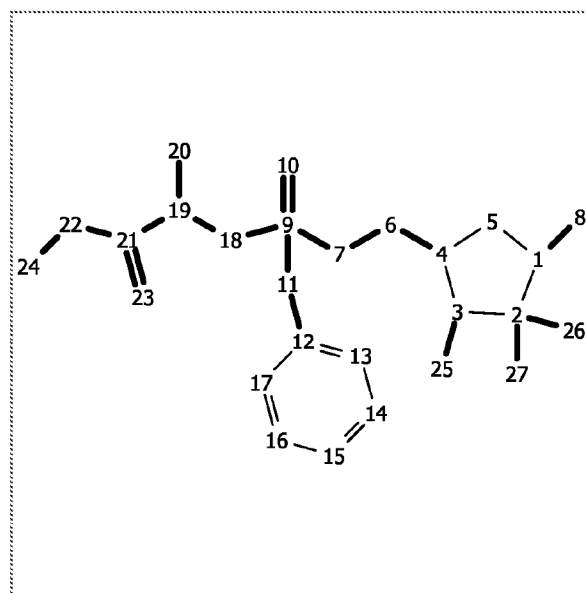
Structure Details (17077267-str5)

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Ring Bonds

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Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 12, 13, 14, 15, 16, 17	Ring				
6, 7, 9, 10, 11, 19, 21, 22, 23, 26, 27	Chain				

Bond Attributes

Bond	Type	Value
12-13, 13-14, 14-15, 15-16, 16-17, 17-12	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1	Ring	Exact/Normalized
2-26, 2-27, 4-6, 19-20, 19-21, 22-24	Chain	Exact
1-8, 3-25, 6-7, 7-9, 9-10, 9-11, 9-18, 11-12, 18-19, 21-22, 21-23	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 8, 12, 13, 14, 15, 16, 17	Atom	Limited
6, 7, 9, 10, 11, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Class	Limited

(FILE 'HOME' ENTERED AT 08:31:08 ON 07 APR 2022)

FILE 'REGISTRY' ENTERED AT 08:31:20 ON 07 APR 2022

L1 STRUCTURE UPLOADED
L2 50 S L1 SSS SAM
L3 12573 S L1 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:36:46 ON 07
APR 2022

L4 10079 S L3
L5 4245 S L4 AND "HCV"
L6 785 S L5 AND PRODRUG
L7 372 S L6 AND PURINE
L8 0 S L7 AND ADENOSIEN
L9 111 S L7 AND ADENOSINE

FILE 'REGISTRY' ENTERED AT 08:39:12 ON 07 APR 2022

L10 STRUCTURE UPLOADED
L11 6 S L10 SSS SAM
L12 131 S L10 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:41:36 ON 07
APR 2022

L13 83 S L12
L14 82 S L13 AND ("HCV" OR "HEPATITIS C")

FILE 'REGISTRY' ENTERED AT 08:57:29 ON 07 APR 2022

L15 STRUCTURE UPLOADED
L16 40 S L15 SSS SAM
L17 871 S L15 SSS FULL

FILE 'CAPLUS, MEDLINE, USPATFULL, USPAT2' ENTERED AT 08:58:43 ON 07
APR 2022

L18 518 S L17
L19 228 S L18 AND HCV

=>

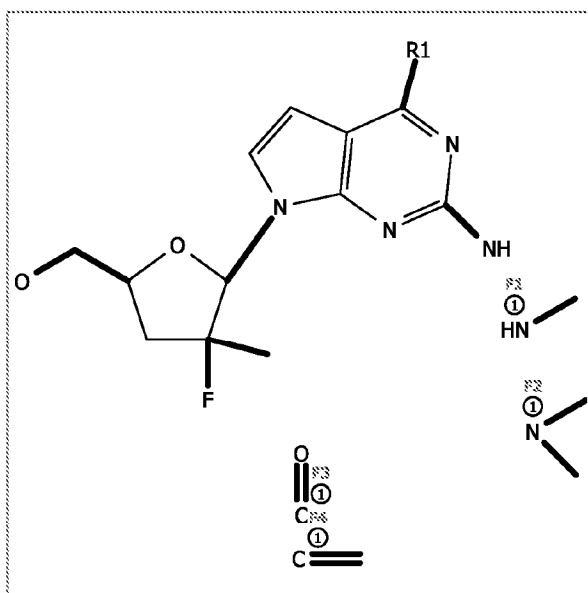
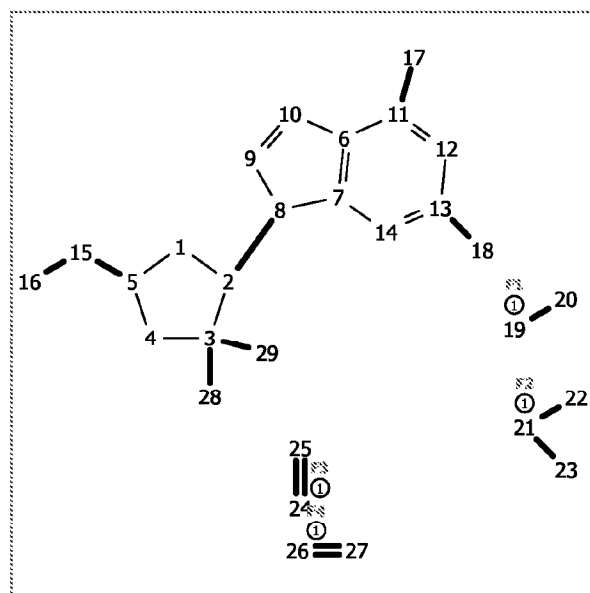
Structure Details (17077267-str2)

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



R-group Definitions

R-group	Values
R1	H, X, OH, NH2, F1, F2, F3, F4

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

Node	Type	H Count	Non H Count	Mass	Valency
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Ring				
15, 16, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29	Chain				

Bond Attributes

Bond	Type	Value
6-7, 6-11, 11-12, 12-13, 13-14, 14-7	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1, 7-8, 8-9, 9-10, 10-6	Ring	Exact/Normalized
26-27	Chain	Exact
3-28, 3-29, 5-15, 8-2, 11-17, 13-18, 15-16, 19-20, 21-22, 21-23, 24-25	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Atom	Limited
15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29	Class	Limited

<i>Search Notes</i> 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 (see attached)	04/07/2022	/PL/
Inventor, Updated REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 searches	09/16/2022	/PL/

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du et al.
				Art Unit	1623
				Examiner Name	Patrick T. Lewis
Sheet	1	of	1	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2004113360	12-29-2004	G NAUCHNY TS VIRUSOLOGII BIO		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Blanver's Third-party Opinion Brief in Brazilian Patent Application No. PI0809654-6 dated December 18, 2020. 26 pages	
		Erti et al. A comparative study of the in vitro and in vivo antiviral activities of acyclovir and penciclovir. Antiviral Chemistry & Chemotherapy. 1995, 6(2), 89-97, page 89, left column, "Summary", pages 89-93, section "Results", pages 93,94, section "Discussion".	
		Office Action and Search Report for Chinese Patent Application No. 201811280509.0 dated March 3, 2022. 22 pages	
		Office Action for Chinese Patent Application No. 201811280064.6 dated April 2, 2022. 13 pages	
		Office Action for Chinese Patent Application No. 201811348434.5 dated April 2, 2022. 12 pages	
		Official Action for Argentinian Patent Application No. 20170103608 dated January 26, 2022. 6 pages	
		Official Action for Russian Patent Application No. 2018103329 dated May 24, 2021. 26 pages	
		Opposition by Mr. Yellajyosula Lakshmi Narasimha Murthy dated October 28, 2021. 17 pages	
		Rejection Resolution for Argentinean Patent Application No. 20120100340 dated May 31, 2022. 16 pages	

Examiner Signature	/PATRICK T LEWIS/	Date Considered	09/15/2022
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language translation is attached.

SMRH:4859-2833-9753.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237
117796	7590	09/22/2022		
Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626			EXAMINER LEWIS, PATRICK T	
			ART UNIT	PAPER NUMBER
			1623	
			NOTIFICATION DATE	DELIVERY MODE
			09/22/2022	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SheppardMullin_Pair@firsttofile.com
ipdocketing@gilead.com
svipdocketing@sheppardmullin.com

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Applicant's Response Dated July 12, 2022

2. In the Response dated July 12, 2022, claims 17-19 were amended. Claims 13-19 are pending. An action on the merits of claims 13-19 is contained herein.

3. The rejection of claims 17-19 under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, has been rendered moot in view of applicant's Amendment dated July 12, 2022.

4. The rejection of claims 13-15 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clark WO 2005/003147 A2 (Clark) and Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (Perrone) in combination is maintained for the reasons of record as set forth in the Office Action dated April 12, 2022.

5. Amended claim 19 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clark WO 2005/003147 A2 (Clark) and Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (Perrone) in combination for the reasons of record as applied to claims 13-15 in the last Office Action dated April 12, 2022 and is not repeated separately.

6. The rejection of claim 16 under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clark WO 2005/003147 A2 (Clark) and Perrone et al. J. Med. Chem. (2007), Vol. 50,

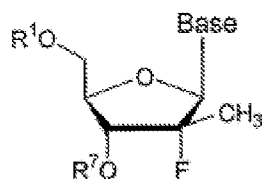
pages 1840-1849 (Perrone) in combination has been withdrawn upon further consideration. The combination of Clark and Perrone does not reasonably teach or suggest a compound wherein: (a) R⁴ is -CH₃, ethyl, n-propyl or i-propyl; (b) R¹⁰ is -NHR' and R¹¹ is -NH₂; and (c) R' is C₁₋₆ alkyl.

Rejections Set Forth in the Office Action Dated April 12, 2022

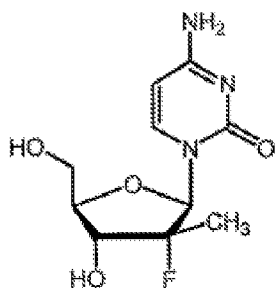
7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
8. Claims 13-15 and 19 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Clark WO 2005/003147 A2 (Clark) and Perrone et al. J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (Perrone) in combination.
9. Applicant's arguments filed July 12, 2022 have been fully considered but they are not persuasive. Applicant submits that the Office has not established prima facie case of obviousness as the standard employed in the Office Action is incorrect. Applicant asserts that under the standard established by Federal Circuit case law, a lead compound analysis is required when determining obviousness for chemical compounds. Applicant argues that the claimed compounds of formula I-6 are not obvious under the lead compound analysis. Applicant further argues impermissible hindsight and that there would not have been a reasonable expectation of success.

The examiner respectfully disagrees.

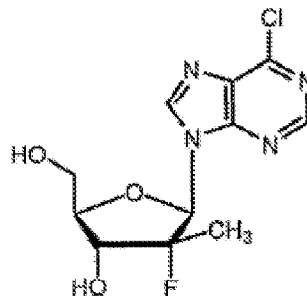
While the genus of Clark potentially embraces a large number of compounds, the structural diversity of the compounds explicitly disclosed/exemplified is relatively small. The compounds explicitly disclosed/exemplified are all of the formula:



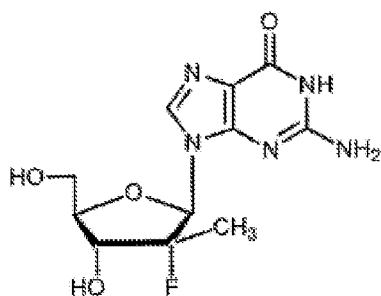
Clark discloses the following structurally complete nucleosides (e.g., parent compound):



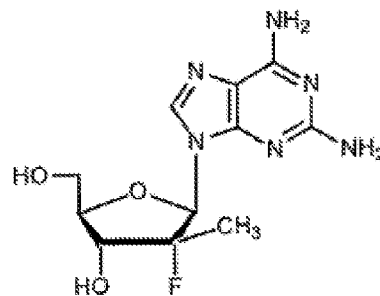
(page 39),



(page 40),



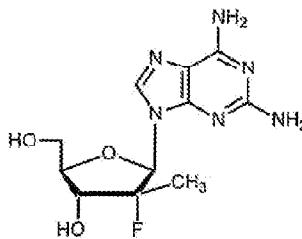
(page 41), and



(page

42), All of the other compounds explicitly disclosed/exemplified by Clark are phosphoric acid derivatives of said parent compound(s) (pages 43-45), prodrugs of said parent compound(s) (pages 60-61), or pharmaceutically acceptable salts of said parent compound(s) (page 87). It would have been prima facie obvious to one of ordinary skill in the art to select any one of the limited number of parent compounds disclosed by Clark as a "lead compound" as those were the compounds selected by Clark for further modification.

Regarding applicant's argument that one of ordinary skill in the art would not be motivated to make the required modifications to arrive at the claimed compounds based on the disclosure of any of the cited art because there is no reasonable expectation of success, obviousness does not require absolute predictability. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. As set forth on pages 8-9 of the last Office Action, it would have been obvious to one of ordinary skill in the art at the time of the invention to provide the anti-HCV compounds of Clark, e.g.



as a prodrug/prodrug wherein the H of the 5'-OH moiety is replaced by a phosphoramidate moiety of Perrone. One would have been motivated to do so in order to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside as suggested by Clark. One would have had a reasonable expectation of success in view of Perrone's teaching that by incorporating such a moiety low or sub-micromolar activity against HCV was achieved.

As set forth on pages 6-7 of the last Office Action, Perrone discloses that a number of compounds showed sub-micromolar inhibition of HCV in cell culture without detectable cytotoxicity. These results confirm that phosphoramidate ProTides can deliver monophosphates of ribonucleoside analogues and suggest a potential path to the generation of novel antiviral agents against HCV infection. Perrone's aryloxy

phosphoramidate ProTide approach allows bypass of the initial kinase dependence by intracellular delivery of the monophosphorylated nucleoside analogue as a membrane permeable "ProTide" form (page 1840). This technology greatly increases the lipophilicity of the nucleoside monophosphate analogue with a consequent increase of membrane permeation and intracellular availability. Previously the approach was successfully demonstrated with the aryloxy-phosphoramidate derivatives of ddA, d4T, LCd4A, and d4A. These nucleotide monophosphate analogues were shown to exhibit greatly enhanced activity against HIV compared to the parent nucleoside analogues in vitro.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Thus, the rejection is maintained in view of the preponderance of evidence.

Conclusion

10. Claims 13-19 are pending. Claims 13-15 and 19 are rejected. Claims 16-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PATRICK T LEWIS whose telephone number is (571)272-0655. The examiner can normally be reached Monday to Friday, 10 AM to 4 PM EST (Maxi Flex).

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at <http://www.uspto.gov/interviewpractice>.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: <https://patentcenter.uspto.gov>. Visit <https://www.uspto.gov/patents/apply/patent-center> for more information about Patent Center and <https://www.uspto.gov/patents/docx> for information about filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/PATRICK T LEWIS/
Primary Examiner, Art Unit 1623

/PL/

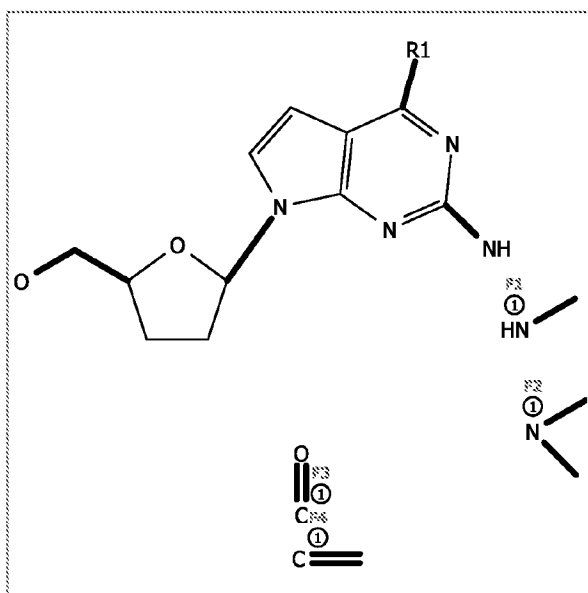
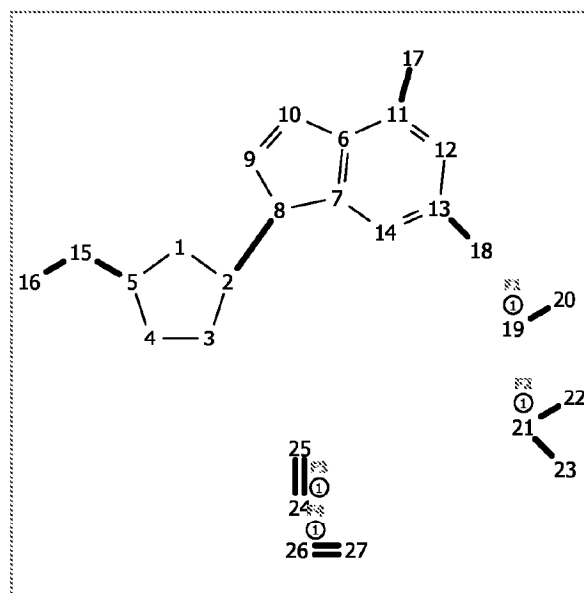
Structure Details (17077267-str1)

Chain Bonds

-  Chain Only
-  Ring or Chain
-  Ring Only

Ring Bonds

-  Closed to ring formation
-  Open to ring formation



R-group Definitions

R-group	Values
R1	H, X, OH, NH2, F1, F2, F3, F4

Node Attributes

Only nodes with attributes changed from the default value of 'Any' are included in this table.

Nodes which do not support these attributes (R-groups, shortcuts and VAP center points) are not included in this table.

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Bond Attributes

Bond	Type	Value
6-7, 6-11, 11-12, 12-13, 13-14, 14-7	Ring	Normalized
1-2, 2-3, 3-4, 4-5, 5-1, 7-8, 8-9, 9-10, 10-6	Ring	Exact/Normalized
26-27	Chain	Exact
5-15, 8-2, 11-17, 13-18, 15-16, 19-20, 21-22, 21-23, 24-25	Chain	Exact/Normalized

Markush Attributes

Nodes which do not support these attributes (R-groups and VAP center points) are not included in this table.

Node	Match Level	Element Count Level
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14	Atom	Limited
15, 16, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27	Class	Limited



ELECTRONIC PAYMENT RECEIPT

APPLICATION #
17/077,267

RECEIPT DATE / TIME
11/15/2022 09:29:19 PM ET

ATTORNEY DOCKET #
37JD-199059-US13

Title of Invention

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4237	FILED BY	Joannah Lalueces
PATENT CENTER #	61184348	AUTHORIZED BY	Joy Nemirow
CUSTOMER #	117796	FILING DATE	10/22/2020
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Jinfa Du

Payment Information

PAYMENT METHOD DA / 504561	PAYMENT TRANSACTION ID E2022AEL31184460	PAYMENT AUTHORIZED BY Joannah Lalueces
PRE-AUTHORIZED ACCOUNT 504561	PRE-AUTHORIZED CATEGORY 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.21 (Miscellaneous fees and charges)	

FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	260.00	1	260.00
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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du
				Art Unit	1623
				Examiner Name	Patrick T. Lewis
Sheet	1	of	1	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2008104408	09-04-2008	K. U. LEUVEN RESEARCH & DEVELOPMENT		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Examination Report for Australian Application No. 2021202327 dated August 18, 2022. 9 pages	
		Office Action for Chinese Application No. 201811280509.0 dated October 13, 2022. 13 pages	

Examiner Signature		Date Considered	
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gilead Sciences, Inc.

Application No.: 17/077,267

Confirmation No.: 4237

Filed: October 22, 2020

Art Unit: 1623

For: NUCLEOSIDE PHOSPHORAMIDATE
PRODRUGS

Examiner: Patrick T. Lewis

INFORMATION DISCLOSURE STATEMENT (IDS)

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

Pursuant to 37 C.F.R. §§ 1.56, 1.97, and 1.98, the attention of the United States Patent and Trademark Office is hereby directed to the references listed on the attached PTO/SB/08. It is respectfully requested that the information be expressly considered during the prosecution of the above-identified application, and that the references be made of record therein and appear among the “References Cited” on any patent to issue therefrom.

This Information Disclosure Statement is filed after the mailing date of either a Final Action under 37 C.F.R. § 1.113, a Notice of Allowance under 37 C.F.R. § 1.311, or an action that otherwise closed prosecution in this application, but on or before payment of the Issue Fee (37 C.F.R. § 1.97(d)).

Pursuant to 37 C.F.R. § 1.97(e)(1), each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Information Disclosure Statement.

In accordance with 37 C.F.R. § 1.98(a)(2)(ii), copies of U.S. patents and U.S. patent application publications are not submitted. Submitted herewith are copies of foreign patent and non-patent literatures in accordance with 37 C.F.R. § 1.98(a)(2).

In accordance with 37 C.F.R. § 1.97(g), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made. In accordance with 37 C.F.R. § 1.97(h), the filing of this Information Disclosure Statement shall not be construed to be an admission that the information cited in this Information Disclosure Statement is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

It is submitted that the Information Disclosure Statement is in compliance with 37 C.F.R. § 1.98, and the Examiner is respectfully requested to consider the listed references.

Please charge our Deposit Account No. 50-4561 in the amount of \$260.00 covering the fee set forth in 37 C.F.R. § 1.17(p). The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 50-4561.

Respectfully submitted,

Dated: November 15, 2022

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/077,267

RECEIPT DATE / TIME
11/15/2022 09:29:19 PM ET

ATTORNEY DOCKET #
37JD-199059-US13

Title of Invention

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4237	FILED BY	Joannah Laluces
PATENT CENTER #	61184348	FILING DATE	10/22/2020
CUSTOMER #	117796	FIRST NAMED INVENTOR	Jinfa Du
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Joy Nemirow

Documents

TOTAL DOCUMENTS: 6

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
37JD-199059-US13_IDS_SB08.pdf	1	Information Disclosure Statement (IDS) Form (SB08)	123 KB
Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.			
37JD-199059-US13_Amendment_After_Final_Office_Action.pdf	6	Response After Final Action	161 KB
ExaminationReport_AU2021202327_2022-08-18.pdf	9	Non Patent Literature	139 KB
OfficeAction_CN2018112805	13	Non Patent Literature	544 KB

090_2022-10-13.pdf

WO2008104408.pdf	74	Foreign Reference	3196 KB
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37JD-199059-US13_IDS_Transmittal_Letter.pdf	2	Transmittal Letter	95 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
4 September 2008 (04.09.2008)

PCT

(10) International Publication Number
WO 2008/104408 A2(51) International Patent Classification: **Not classified**(21) International Application Number:
PCT/EP2008/001764(22) International Filing Date:
27 February 2008 (27.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0703715.3 27 February 2007 (27.02.2007) GB
0703722.9 27 February 2007 (27.02.2007) GB
0718228.0 17 September 2007 (17.09.2007) GB
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),

[Continued on next page]

(54) Title: PHOSPHATE MODIFIED NUCLEOSIDES USEFUL AS SUBSTRATES FOR POLYMERASES AND AS ANTIVIRAL AGENTS

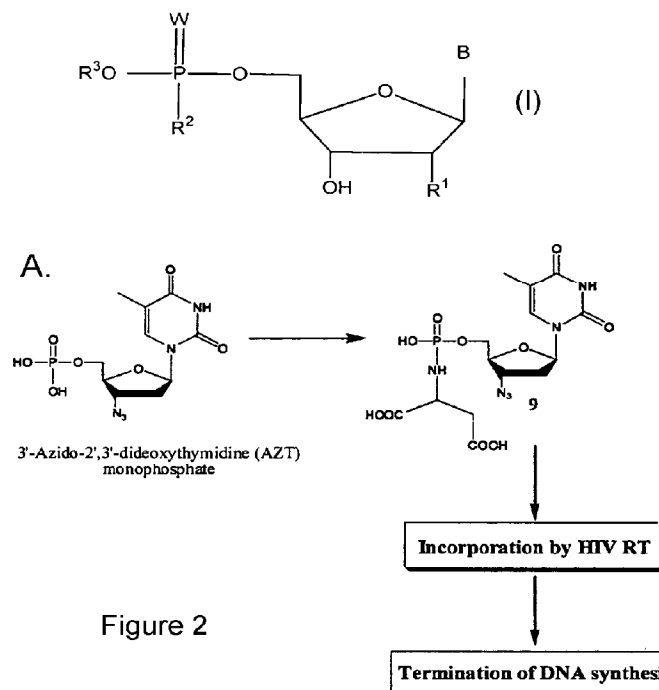


Figure 2

(57) Abstract: This invention provides phosphate-modified nucleosides represented by the structural formula: wherein - B is a pyrimidine or purine base, or an analogue thereof, optionally substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, methyl, ethyl, amino and methylamino; - R¹ is H or OH; - R³ is selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl-C₁₋₆alkyl and 2-cyanoethyl, wherein said C₁₋₆ alkyl, C₃₋₆ cycloalkyl or aryl-C₁₋₆alkyl is optionally substituted with one or more, preferably 1, 2 or 3, substituents independently selected from the group consisting of halogen, OH, C₁₋₆ alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano and amino; - W is O or S; and - R² is a group derived from an amino-acid. These compounds are useful as substrates for DNA/RNA polymerases, and as anti-viral agents.

WO 2008/104408 A2



European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

Declaration under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

PHOSPHATE MODIFIED NUCLEOSIDES USEFUL AS SUBSTRATES FOR
POLYMERASES AND AS ANTIVIRAL AGENTS

FIELD OF THE INVENTION

5 The present invention relates to novel phosphate-modified nucleosides, such as amino acid phosphoramidate nucleosides. The present invention also relates to the phosphate-modified nucleosides as substrates for wild type and/or mutated DNA or RNA polymerases.

10 The present invention provides for the use of these novel phosphate-modified nucleosides for the production of oligonucleotides such as DNA or RNA and of polypeptides or proteins. The invention also relates to the use of these phosphate-modified nucleosides for growing or selecting specific micro-organisms, such as bacteria. The invention further provides for the use of these novel phosphate-modified nucleosides to treat or prevent viral infections and their use to manufacture
15 a medicine to treat or prevent viral infections, particularly infections with viruses belonging to the HIV family.

 The present invention furthermore relates to a method for the production of oligonucleotides, peptides or proteins by using said phosphate-modified nucleosides.

20 BACKGROUND OF THE INVENTION

 There has been significant progress in the design and synthesis of numerous nucleotide analogues bearing a modified nucleobase moiety or unnatural sugar and that are substrates for polymerases. Modifications at the phosphate moiety are introduced to increase the stability of a nucleotide toward enzymatic degradation or to
25 mask the phosphate negative charge and facilitate its penetration into a cell. Common strategy in nucleotide prodrug design is protecting a phosphate moiety with a labile masking group. Removal of a masking group liberates a nucleoside monophosphate entity to be transformed into a nucleoside triphosphate (hereinafter referred as NTP), a substrate for intracellular enzymes. However, even after removal
30 of the masking group, phosphorylation and activation of nucleoside monophosphate remains a problem due to substrate specificity of cellular kinases. Therefore, design of a nucleotide analogue that would allow bypassing the kinase activation pathway while behaving as a direct polymerase substrate would be a considerable challenge.

 Treatment of certain viral infections has always been a challenging task due to
35 ability of some viruses to integrate into a host's genome. Therefore, the viral enzymes

that are critical for viral genome replication and integration are regarded as the most effective targets for the design of anti-viral agents.

A lot of attention has been given to studying mechanisms of action of Human Immunodeficiency Virus (type 1) (HIV-1) and developing specific inhibitors towards this very challenging and important target. One of the enzymes that are essential for the HIV replication is HIV reverse transcriptase (HIV RT). The function of this enzyme is to use a viral RNA genome and a reverse transcriptase to synthesize a double stranded DNA for integration into a host genome. Because this step is critical for the propagation of the viral infection, HIV reverse transcriptase (RT) is an excellent target for anti-viral treatment. Currently, two major classes of RT inhibitors (RTIs) exist and are administered for treatment of HIV infection. Non-nucleoside reverse transcriptase inhibitors (NNRTs) are a group of compounds that act through the allosteric inhibition by binding to a hydrophobic site, or a pocket in close proximity to the active site of HIV RT. The other group of RTIs is represented by nucleoside reverse transcriptase inhibitors (NRTIs) that bind directly to the active site and interfere with the polymerization reaction and DNA synthesis.

Nucleoside reverse transcriptase inhibitors are designed to be recognized as substrates for RT and incorporated into a growing strand for further termination of chain elongation. Inhibition of reverse transcriptase activity and chain termination by NRTIs is achieved by introduction of structural modifications to the sugar moiety. The elongation of the DNA strand by a polymerase requires a nucleophilic attack of the 3'-OH group to the α phosphorus atom of an incoming nucleotide. Therefore, nucleoside analogs that lack the 3'-OH group or have it substituted with other functional groups (for instance, N_3 , F, H) not capable of the nucleophilic attack and formation of phosphodiester bond would act as chain terminators.

Termination of DNA or RNA synthesis with nucleoside analogues is a common and one of the most efficient strategies in the treatment of viral infections, regardless of various side effects and cell toxicity. The therapeutically active form of a nucleoside analogue is a nucleoside triphosphate. However, at the physiological pH nucleoside triphosphates are negatively charged molecules and thus they can not penetrate cellular membranes. Hence, RT inhibitors are usually administered as biologically inactive free nucleosides or as monophosphate prodrugs where a phosphate group is masked with a lipophilic group.

There are three steps of kinase-mediated activation of anti-viral nucleosides. At first, transformation to a monophosphate derivative takes place through the action of a cytoplasmic nucleoside kinase (for instance, thymidine kinase and deoxycytidine

kinase). Furthermore, a nucleoside 5'-monophosphate kinase catalyzes the conversion of a nucleoside monophosphate to a nucleoside diphosphate. Finally, a diphosphate derivative is phosphorylated by a nucleoside 5'-diphosphate kinase (NDK) to provide an anti-viral nucleoside analog in its activated (phosphorylated) form. The efficiency of phosphorylation depends on substrate specificity of kinases. For instance, in the case of the AZT phosphorylation cascade, conversion from the nucleoside monophosphate to the nucleoside diphosphate becomes a rate limiting step as thymidylate kinase (TMPK) catalyzes this conversion significantly slower than in the case of the natural substrate (TMP). The consequences of this inefficiency are accumulation of AZTMP in the cytosol and decreased therapeutic concentration of AZTTP, the activated nucleoside form. However, it was determined that high levels of AZTMP have an inhibitory effect on thymidylate kinase by competing with its natural substrate (TMP) and resulting in reduced levels of TDP and TTP. Moreover, increased levels of AZT and its phosphorylated derivatives also affect other enzymes of the *de novo* dNTPs synthesis resulting in skewed natural nucleotide concentrations.

Therefore, administration of free NRTIs, which often relies on intracellular phosphorylation and activation, has significant drawbacks. One of the possible solutions is a prodrug or pronucleotide approach. In the prodrug approach, the monophosphate moiety is "masked" with a labile functional group which also serves to facilitate passage of a "masked" nucleotide inside the cell. Once inside the cell, a masking group is removed either enzymatically or through chemical activation. Removal of the masking group affords a free nucleoside monophosphate intracellularly where it can be further phosphorylated by TMPK and NDK. Thus, although the prodrug approach facilitates delivery of an inhibitory nucleoside inside the cell and eliminates the need for initial phosphorylation by a nucleoside kinase, phosphorylation by TMPK and NDK are still required.

Besides delivery and bio-distribution challenges, another drawback that is often associated with anti-viral therapy is emergence of resistant strains. In the case of HIV-1, the drug resistance is developed by appearance of mutations that would allow HIV RT to discriminate NRTIs for natural nucleotides or remove an incorporated unnatural nucleobase by excision reactions. It has also been shown for herpes simplex virus (HSV) that reduction in anti-herpetic activity of acyclovir, a drug activated by thymidine kinase phosphorylation and commonly used for treatment of HSV infections, is mostly associated with thymidine kinase dependent resistance. Established strategies to manage acyclovir-resistant HSV infections include

administration of anti-viral drugs acting directly on a viral DNA polymerase (foscarnet, cidifovir) or by modulating immune response of a patient. However, the later approach is not always feasible and the former one could worsen patient's condition since these medications impose a significant level of toxicity.

- 5 Therefore, considering all aforementioned aspects of therapy directed to inhibit viral polymerases and reverse transcriptases, a nucleotide analogue that would not depend on activation by nucleoside/nucleotide kinases whilst serving as a natural substrate mimic, would be of a great interest.

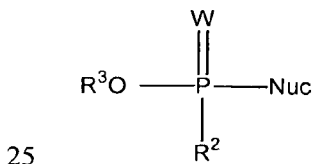
10 SUMMARY OF THE INVENTION

The present invention provides novel phosphate-modified nucleosides which can act as substrates of DNA- or RNA-polymerases and/or as antiviral agents.

- The present invention provides novel phosphate-modified nucleosides that can be used as alternative (compared to natural NTPs or dNTPs) substrates for DNA-
 15 or RNA-polymerases. In a particular embodiment, these phosphate-modified nucleotides are such that the pyrophosphate group of nucleosides/nucleotides is replaced by a good leaving group, more particularly a leaving group in a nucleotidyl transfer mechanism. In a specific embodiment of the invention, this leaving group is an amino acid coupled by a phosphoramidate binding, yet more particularly this amino
 20 acid may be Asp or His, or a close variant thereof.

DETAILED DESCRIPTION OF THE INVENTION

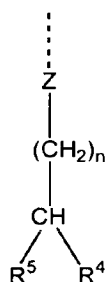
According to one embodiment, EMBED the present invention encompasses phosphate-modified nucleosides of the general formula A



wherein

- Nuc is a natural nucleoside or a nucleoside analogue, wherein said natural nucleoside or nucleoside analogue can be substituted or unsubstituted, thereby creating a phosphonate or phosphate comprising compound;
- 30 - R³ is independently selected from H; (C₁-C₆)alkyl; (C₃-C₆)cycloalkyl; aryl-(C₁-C₆)alkyl; and 2-cyanoethyl; wherein any alkyl, cycloalkyl or arylalkyl may optionally be substituted with 1, 2 or 3 halogen, OH, (C₁-C₆)alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, or amino;

- W is independently selected from O or S; and
- R² is a group represented by the structural formula V



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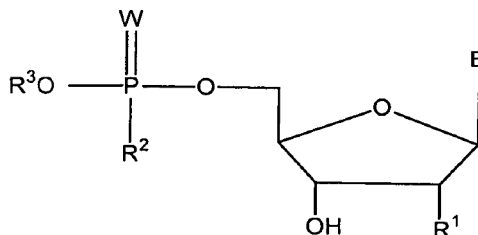
wherein

- n is 0 or 1;
- Z is selected from O; S; or NH;
- each of R⁴ and R⁵ are independently selected from (CH₂)_m-COOR⁶ and (CH₂)_m-imidazolyl;
- R⁶ is selected from H or (C₁-C₆)alkyl;
- m is selected from 0, 1, and 2.

10

According to a more specific embodiment of this invention, said natural Nucleoside (Nuc) is coupled via its 5' position to P in formula A.

- 15 Another embodiment of the present invention relates to phosphate-modified nucleotides as defined in claim 1, i.e. with reference to the structural formula (I):



wherein

- B is a pyrimidine or purine base, or an analogue thereof, optionally substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, methyl, ethyl, isopropyl, amino, methylamino, ethylamino, trifluoromethyl and cyano;
- R¹ is H or OH;
- R³ is selected from the group consisting of H, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl-C₁₋₆alkyl and 2-cyanoethyl, wherein said C₁₋₆ alkyl, C₃₋₆ cycloalkyl or aryl-C₁₋₆ alkyl is optionally substituted with one or more, preferably 1, 2 or

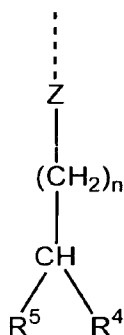
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3, substituents independently selected from the group consisting of halogen, OH, C₁₋₆ alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano and amino;

- W is O or S; and

5 - R² is a group represented by the structural formula IV:



wherein

- n is 0 or 1;

- Z is selected from the group consisting of O, S, NH and NCH₃;

10 - each of R⁴ and R⁵ is independently selected from the group consisting of hydrogen, (CH₂)_m-COOR⁶; and (CH₂)_m-imidazolyl, provided that R⁴ and R⁵ are not both hydrogen;;

- R⁶ is H or C₁₋₆ alkyl;

- m is 0, 1 or 2; and

15 - dotted lines represent the point of attachment of Z to the phosphorous atom of formula (III);

stereoisomers, pharmaceutically acceptable salts and pro-drugs thereof, provided that said phosphate-modified nucleoside is not:

- N-5'-adenylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,

20 - N-5'-uridylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,

- N-5'-thimidylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,

- N-5'-adenylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,

25 - N-5'-guanylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,

- N-5'-uridylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,

- N-5'-thymidylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,

- N-5'-citidylylphosphoramidate L-aspartic acid disodium salt,
- N-5'-uridylylphosphoramidate L-histidine
- N-5'-uridylylphosphoramidate L-histidine 1-methyl ester,
- N-5'-adenylylphosphoramidate L-histidine 1-methyl ester,
- 5 - N-5'-cytidylylphosphoramidate L-histidine 1-methyl ester, or
- N-5'-uridylylphosphoramidate L-aspartic acid.

In formula I, W is preferably O but it can be replaced by S by chemical reactions known in the art. According to another embodiment of the invention, the molecular weight of R₂ is not above 500.

10 In a particular embodiment, the present invention also relates to the phosphate-modified nucleosides of formula I wherein R¹, R², R³ and W have any of the values as described herein, and wherein B is adenine; guanine; cytosine; thymine; uracil, or a substituted uracil as described below.

In a particular embodiment, the present invention also relates to the
15 phosphate-modified nucleosides of formula I wherein B, R¹, R² and W have any of the values as described herein, and wherein R³ is H.

In a particular embodiment, the present invention also relates to the phosphate-modified nucleosides of formula I wherein B, R¹, R² and R³ have any of the values as described herein, and wherein W is O.

20 In a particular embodiment, the present invention also relates to the phosphate-modified nucleosides of formula I wherein B, R², R³ and W have any of the values as described herein, and wherein R¹ is H; and in another particular embodiment, the present invention also relates to the phosphate-modified nucleoside of formula I wherein B, R², R³ and W have any of the values as described herein, and
25 wherein R¹ is OH.

In a particular embodiment, the present invention also relates to the phosphate-modified nucleosides of formula I wherein B, R¹, R², R³ and W have any of the values described herein, and wherein n is 0.

In a particular embodiment, the present invention also relates to the
30 phosphate-modified nucleosides of formula I wherein R¹, R², R³ and W have any of the values described herein, and wherein B is a pyrimidine or purine base analogue as described in the Definitions section below, in particular 5-azapyrimidine, 5-azacytosine, 7-deazapurine, 7-deazaadenine, 7-deazaguanine, or 7-deaza-8-azapurines.

35 In a particular embodiment of the foregoing, the present invention also relates to the phosphate-modified nucleoside of formula I wherein B, R¹, R³ and W have any

of the values as described herein, and wherein R^2 is a nitrogen-linked natural or synthetic amino acid; and in another particular embodiment, said amino acid is linked via its α -NH₂ group. In yet another particular embodiment, said amino acid is linked via its α -NH₂ group, whereby the H group of the NH-linking group is substituted by a methyl group.

In a more particular embodiment of the invention, said amino acid is selected from Asp or His. In another particular embodiment of the invention, said amino acid is selected from the group consisting of L-alanine, D-alanine, beta-alanine and N-methyl beta-alanine (3-(methylamino)propionic acid).

In yet another particular embodiment of the invention, said amino acid is in the L conformation.

In another particular embodiment of the invention, with reference to formula (IV), Z is O; NH or NCH₃.

In yet another particular embodiment of the invention, R^4 is COOH and R^5 is selected from CH₂-COOH or CH₂-4-imidazolyl.

In a yet more particular embodiment of the invention, R^3 is H and R^2 is according to formula IV, wherein Z is NH or NCH₃, R^4 is COOH and R^5 is CH₂-COOH or CH₂-4-imidazolyl.

In yet another particular embodiment, the present invention relates to phosphate-modified nucleosides according to formula I, wherein R^3 is H and R^2 is an amino acid coupled to the phosphor atom through its amino function, more particularly said amino acid is Aspartic acid (Asp), Histidine (His), methyl-aspartic acid.

In a particular embodiment, the novel phosphate-modified nucleoside is 2'-deoxy-adenosine-5'-aspartyl-phosphoramidate (Asp-dAMP), 2'-deoxy-cytidine-5'-aspartyl-phosphoramidate (Asp-dCMP), 2'-deoxy-guanosine-5'-aspartyl-phosphoramidate (Asp-dGMP), 2'-deoxy-thymidine-5'-aspartyl-phosphoramidate (Asp-dTMP), 2'-deoxy-uridine-5'-aspartyl-phosphoramidate (Asp-dUMP), 2'-deoxyadenosine-5'-N-methylaspartyl-phosphoramidate; 2'-deoxycytidine-5'-N-methylaspartyl-phosphoramidate, 2'-deoxycytidine-5'-N-methylaspartyl-phosphoramidate, 2'-deoxyguanosine-5'-N-methylaspartyl-phosphoramidate, 2'-deoxythymidine-5'-N-methylaspartyl-phosphoramidate, or 2'-deoxyuridine-5'-N-methylaspartyl-phosphoramidate.

In another particular embodiment, the novel phosphate-modified nucleoside is 2'-deoxy-adenosine-5'-histidyl-phosphoramidate (His-dAMP), 2'-deoxy-cytidine-5'-histidyl-phosphoramidate (His-dCMP), 2'-deoxy-guanosine-5'-histidyl-

phosphoramidate (His-dGMP), 2'-deoxy-thymidine-5'-histidyl-phosphoramidate (His-dTMP), 2'-deoxy-uridine-5'-histidyl-phosphoramidate (His-dUMP), 2'-deoxyadenosine-5'-*N*-methylhistidyl-phosphoramidate, 2'-deoxycytidine-5'-*N*-methylhistidyl-phosphoramidate, 2'-deoxycytidine-5'-*N*-methylhistidyl-phosphoramidate, 2'-deoxyguanosine-5'-*N*-methylhistidyl-phosphoramidate, 2'-deoxythymidine-5'-*N*-methylhistidyl-phosphoramidate, or 2'-deoxyuridine-5'-*N*-methylhistidyl-phosphoramidate.

In another particular embodiment, the novel phosphate-modified nucleoside is adenosine-5'-aspartyl-phosphoramidate (Asp-AMP), cytidine-5'-aspartyl-phosphoramidate (Asp-CMP), guanosine-5'-aspartyl-phosphoramidate (Asp-GMP), 5-methyluridine-5'-aspartyl-phosphoramidate (Asp-m5uMP), uridine-5'-aspartyl-phosphoramidate (Asp-UMP), adenosine-5'-*N*-methylaspartyl-phosphoramidate, cytidine-5'-*N*-methylaspartyl-phosphoramidate, cytidine-5'-*N*-methylaspartyl-phosphoramidate, guanosine-5'-*N*-methylaspartyl-phosphoramidate; uridine-5'-*N*-methylaspartyl-phosphoramidate, or 5-methyluridine-5'-*N*-methylaspartyl-phosphoramidate..

In another particular embodiment, the novel phosphate-modified nucleoside is adenosine-5'-histidyl-phosphoramidate (His-AMP), cytidine-5'-histidyl-phosphoramidate (His-CMP), guanosine-5'-histidyl-phosphoramidate (His-GMP), 5-methyluridine-5'-histidyl-phosphoramidate (His-m5uMP), uridine-5'-histidyl-phosphoramidate (His-UMP), adenosine-5'-*N*-methylhistidyl-phosphoramidate; cytidine-5'-*N*-methylhistidyl-phosphoramidate; cytidine-5'-*N*-methylhistidyl-phosphoramidate; guanosine-5'-*N*-methylhistidyl-phosphoramidate; uridine-5'-*N*-methylhistidyl-phosphoramidate; or 5-methyluridine-5'-*N*-methylhistidyl-phosphoramidate.

A second aspect of the present invention relates to the use of the phosphate-modified nucleosides of formula I, including any above-referred specific embodiments thereof, as a substrate for DNA- or RNA-polymerases, these polymerases being either wild-type (naturally occurring) or mutated according to common knowledge in the art. In a particular embodiment, said DNA- or RNA-polymerases are selected from Terminator DNA polymerase, KF (exo⁻) DNA polymerase, or Reverse Transcriptase (e.g. HIV-RT) or mutated forms of these enzymes. The enzymes as described herein above can be mutated, using common knowledge in the art, in order to adapt (better) to the novel phosphate-modified nucleotide disclosed in this invention.

In a particular embodiment, the phosphate-modified nucleosides of this invention can be used to build in at least 1, 2 or 3 nucleotides in a growing DNA- or RNA-strand.

5 In another particular embodiment, the phosphate-modified nucleosides of this invention can be used to build in at maximum 1, 2 or 3 nucleotides in a growing DNA- or RNA-strand.

10 In yet another particular embodiment, the phosphate-modified nucleosides of this invention can be used with a mixture of natural dNTPs or NTPs (ATP,CTP,GTP,UTP,TTP) as a substrate for DNA/RNA-polymerases, more in particular to built in 1-300 nucleotides in a growing DNA- or RNA-strand.

In yet another particular embodiment, the phosphate-modified nucleosides of this invention can be used with a mixture of natural dNTPs or NTPs (ATP,CTP,GTP,UTP,TTP) as a substrate for DNA/RNA-polymerases, more in particular to built in 2-300 nucleotides in a growing DNA- or RNA-strand.

15 The present invention also relates to the use of the phosphate-modified nucleoside of formula I, including any above-referred specific embodiments thereof, for the (enzymatic) production of oligonucleotides, peptides or proteins.

20 In a particular embodiment, the phosphate-modified nucleosides of the invention, including any above-referred specific embodiments thereof, can be used for *in vitro* production of DNA or RNA. In another particular embodiment, the phosphate-modified nucleosides of the invention, including any above-referred specific embodiments thereof, can also be used for *in vitro* production of peptides or proteins. In another particular embodiment the phosphate-modified nucleosides of the invention, including any above-referred specific embodiments thereof, can be used
25 for PCR (polymerase chain reaction).

In yet another particular embodiment, the phosphate-modified nucleosides of the invention, including any above-referred specific embodiments thereof, can be used as a substrate for the growth of wild type and/or mutated bacteriae. In a particular embodiment, the phosphate-modified nucleotides of the invention, including
30 any above-referred specific embodiments thereof, can be used as a substrate for the growth of bacteriae with mutated DNA/RNA polymerase, preferably wherein the mutation is suitable to adapt (better) to the new substrate.

Another aspect of the invention relates to a pharmaceutical or non-pharmaceutical composition comprising the phosphate-modified nucleosides of the
35 invention, including any above-referred specific embodiments thereof. In a particular embodiment, said non-pharmaceutical composition further comprises one or more

natural NTPs and in yet another particular embodiment, said composition further comprises one or more natural dNTPs.

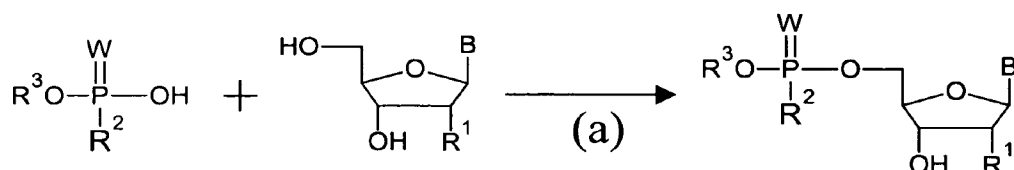
Yet another aspect of the invention relates to a method for the production of oligonucleotides, RNA, DNA, peptides and/or proteins by using the phosphate-modified nucleotides of the invention, including any above-referred specific
5 embodiments thereof.

Another aspect of the present invention relates to compounds represented by formula I, including any above-referred specific embodiments thereof, having antiviral activity, more specifically to these compounds that inhibit the replication of
10 viruses, even more specifically to these compounds that inhibit the replication of HIV-1.

Another aspect of the present invention relates to the compounds of formula I, including any above-referred specific embodiments thereof, for use as a medicine and to the use of said compounds as a medicine, more in particular to the use of said
15 compounds to treat or prevent a viral infection in a mammal, even more particularly to treat or prevent HIV in a mammal such as a human being.

Another aspect of the invention relates to pharmaceutical compositions comprising the compounds of formula I, including any above-referred specific embodiments thereof, in combination with one or more pharmaceutical excipients.
20 The invention further relates to the use of the compounds of formula I, including any above-referred specific embodiments thereof, in the manufacture of a medicament useful for the treatment of viral infections, more specifically for the treatment of HIV-1. The present invention also relates to a method of treatment or prevention of viral infections, by using the compounds of formula I, including any above-referred specific
25 embodiments thereof.

Still another aspect of the invention relates to a process for the preparation of the phosphate-modified nucleosides of the invention. In one embodiment of said aspect, the method comprises the steps of interacting a nucleotide monophosphate (NMP) with the methylester of an amino acid to produce the methyl ester of an amino
30 acid phosphoramidate nucleotide analogue. Deprotection of this nucleotide analogue with a deprotecting agent such as, but not limited to, an alkali hydroxide, e.g. 0.04 M NaOH, provides the desired amino acid phosphoramidate nucleoside of this invention. In an alternative embodiment of said aspect, the process for the preparation of the phosphate-modified nucleosides of the invention comprises the
35 synthetic step as shown in Scheme 1:
Scheme 1,



wherein (a) schematically represents the presence in the reaction mixture of a suitable catalyst for the condensation of the 5'-OH and phosphate acid groups, such as but not limited to an arylsulfonylhalide, e.g. an optionally substituted phenylsulfonylchloride.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a few amino acid phosphoramidates prepared in the following examples. 1. Asp-dAMP, 2. Glu-dAMP, 3 Gly-dAMP, 4. Ala-dAMP, 5. Tyr-dAMP, 6. His-dAMP, 7. Ser-dAMP, 8. Pro-dAMP.

Figure 2A shows a possible activation of AZT monophosphate by aspartyl. Figure 2B shows a possible application of aspartyl phosphoramidate moiety for in vivo delivery and activation of AZT monophosphate.

Figure 3. Panel I: Incorporation of Asp-dAMP (1) by HIV RT. Panel II: Incorporation of methyl ester Asp-dAMP (1a) by HIV RT Reaction conditions: Primer (P1) was 5'-labeled with ^{33}P followed by annealing to a template T1; 125 nM primer/template (P1/T1), [HIV-RT] = 0.03 U/ μL , time intervals: 5, 15, 30, 60, 90, 120 min.

Figure 4. Efficiency of phosphoramidate incorporation by HIV RT. Reaction conditions: Primer (P1) was 5'-labeled with ^{33}P followed by annealing to a template T1; 125 nM primer/template (P1/T1), [HIV-RT] = 0.03 U/ μL , time intervals: 5, 15, 30, 60, 90, 120 min.

Figure 5. Panel I: Incorporation of Asp-dAMP (1) by Terminator DNA polymerase. Panel II: Incorporation of methyl ester Asp-dAMP (1a) by Terminator DNA polymerase. Reaction conditions: Primer (P1) was 5'-labeled with ^{33}P followed by annealing to a template T1; 125 nM primer/template (P1/T1), [Terminator] = 0.03 U/ μL , [primer] = 0.125 μM , time intervals: 5, 15, 30, 60, 90, 120 min.

Figure 6. Efficiency of phosphoramidate incorporation by Terminator DNA polymerase. Reaction conditions: Primer (P1) was 5'-labeled with ^{33}P followed by annealing to a template T1; 125 nM primer/template (P1/T1), [Terminator] = 0.03 U/ μL , [primer] = 0.125 μM , time intervals: 5, 15, 30, 60, 90, 120 min.

Figure 7. Panel I: Incorporation of Asp-dAMP (1) by Taq DNA polymerase. Panel II: Incorporation of Asp-dAMP (1) by Vent (exo-) DNA polymerase. Panel III:

Incorporation of Asp-dAMP (1) by Klenow Fragment (KF) (exo⁻) DNA polymerase. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T1; 125 nM primer/template (P1/T1), [Taq] = 0.005 U/μL, [Vent] = 0.005 U/μL, [KF] = 0.05 U/μL; time points: 5, 15, 30, 60, 90, 120 min.

- 5 Figure 8. Primer extension with amino acid phosphoramidates by HIV RT. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T3; 125 nM primer/template (P1/T3), [AA-dAMP] = 500 μM; [dATP] = 50 μM; [HIV RT] = 0.03 U/μL; time points: 5, 15, 30, 60, 90, 120 min. Blank: 125 nM primer/template (P1/T3), [HIV RT] = 0.03 U/μL, no nucleotide substrate.
- 10 Figure 9. Extension efficiency of HIV reverse transcriptase. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T3; 125 nM primer/template (P1/T3), [AA-dAMP] = 500 μM; [dATP] = 50 μM; [HIV RT] = 0.03 U/μL; time points: 5, 15, 30, 60, 90, 120 min. Blank: 125 nM primer/template (P1/T3), [HIV RT] = 0.03 U/μL, no nucleotide substrate.
- 15 Figure 10. Primer extension with amino acid phosphoramidates by HIV RT. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T5; 125 nM primer/template (P1/T5), [AA-dAMP] = 500 μM; [dATP] = 50 μM; [HIV RT] = 0.03 U/μL; time points: 5, 15, 30, 60, 90, 120 min. Blank: 125 nM primer/template (P1/T5), [HIV RT] = 0.03 U/μL, no nucleotide substrate.
- 20 Figure 11. Primer extension with amino acid phosphoramidates by Terminator DNA polymerase. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T3; 125 nM primer/template (P1/T3), [AA-dAMP] = 500 μM; [dATP] = 50 μM; [Terminator] = 8×10⁻⁴ U/μL; time points: 5, 15, 30, 60, 90, 120 min. Blank: 125 nM primer/template (P1/T3), [Terminator] = 8×10⁻⁴ U/μL, no nucleotide
- 25 substrate.
- Figure 12. Primer extension efficiency of Terminator DNA polymerase. Reaction conditions: Primer (P1) was 5'-labeled with ³³P followed by annealing to a template T3; 125 nM primer/template (P1/T3), [AA-dAMP] = 500 μM; [dATP] = 50 μM; [Terminator] = 8×10⁻⁴ U/μL; time points: 5, 15, 30, 60, 90, 120 min. Blank: 125 nM
- 30 primer/template (P1/T3), [Terminator] = 8×10⁻⁴ U/μL, no nucleotide substrate.
- Figure 13. Structures of amino acid 2'-deoxynucleoside-5'-monophosphate derivatives used in the HIV RT incorporation assays.
- Figure 14. Primer extension with amino acid phosphoramidates by HIV RT. Conditions: Primer (P1 or P2) was 5'-labeled with ³³P followed by annealing to a
- 35 template (T1, T2 or T4). Reactions were carried out with 125 nM primer-template (P1/T1, P1/T2, P1/T4 or P2/T4), [HIV RT] = 0.03 UμL⁻¹, time points: 5, 10, 20, 30, 60,

120 min. Panel I: Incorporation of 12 with P1T1. Panel II: Incorporation of 9 with P1T2. Panel III: Incorporation of 10 with P1T4. Panel IV: Incorporation of 11 with P2T4.

Figure 15. Control experiments. Conditions: Primer P1 was 5'-labeled with ^{33}P followed by annealing to a template (T4, T2, T1 or A). Reactions were carried out with 125 nM primer-template (P1/T4, P1/T2 or P1/T1), $[\text{HIV RT}] = 0.03 \text{ U}\mu\text{L}^{-1}$, time points: 5, 10, 20, 30, 60, 120 min. Panel I: N-Me-Asp-dAMP (12) with P1T4 (A against A). Panel II: L-Asp-dGMP (9) with P1T4 (G against A). Panel III: L-Asp-dTMP (10) with P1T2 (T against C). Panel IV: L-Asp-dCMP (11) with P1T1 (C against T). Panel V: L-Asp-dAMP (1), L-Asp-dGMP (9), L-Asp-dTMP (10), L-Asp-dCMP (11) and dTTP with P1A. $[\text{Asp-dNMP}] = 1 \text{ mM U}\mu\text{L}^{-1}$.

Figure 16. Panel I. Incorporation of compounds 9 and 1 by HIV RT. Panel II. Control experiment. Incorporation of 9 by HIV RT. Reaction conditions: Primer P1 was 5'-labeled with ^{33}P followed by annealing to a template T2; 125 nM P1T2; $[\text{HIV RT}] = 0.03 \text{ U}\mu\text{L}^{-1}$.

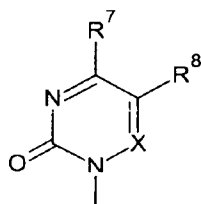
DEFINITIONS

The term " nucleoside analogue " as used herein refers to known nucleoside modifications wherein the sugar ring is modified or removed and therefore also comprises acyclic nucleosides. Nucleoside analogue examples wherein the natural sugar moiety is modified include but are not limited to hexitol nucleic acid (HNA), cyclohexene nucleic acids (CeNA), locked nucleic acids (LNA), altritol nucleic acids (ANA) and peptide nucleic acids (PNA).

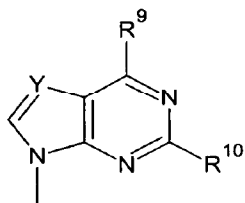
The term " pyrimidine and purine bases " as used herein includes, but is not limited to, adenine, thymine, cytosine, uracyl, guanine and 2,6-diaminopurine and analogues thereof. A purine or pyrimidine base as used herein includes a purine or pyrimidine base found in naturally occurring nucleosides as mentioned above. An analogue thereof is a base which mimics such naturally occurring bases in such a way that their structures (the kinds of atoms and their arrangement) are similar to the naturally occurring bases but may either possess additional or lack certain of the functional properties of the naturally occurring bases. Such analogues include those derived by replacement of a CH moiety by a nitrogen atom (e.g. 5-azapyrimidines such as 5-azacytosine) or vice versa (e.g., 7-deazapurines, such as 7-deazaadenine or 7-deazaguanine) or both (e.g., 7-deaza, 8-azapurines). By derivatives of such bases or analogues are meant those bases wherein ring substituents are either incorporated, removed, or modified by conventional substituents known in the art,

e.g. halogen, hydroxyl, amino, (C₁-C₆)alkyl and others. Such purine or pyrimidine bases, and analogues thereof, are well known to those skilled in the art, e.g. as shown at pages 20-38 of WO 03/093290 .

- In particular purine and pyrimidine analogues B for the purpose of the present invention may be selected from the group comprising pyrimidine bases represented by the structural formula (B):



and purine bases represented by the structural formula (D):



- wherein:

R⁷ and R⁹ are independently selected from the group consisting of H, -OH, -SH, -NH₂, and -NH-Me;

R⁸ and R¹⁰ are independently selected from the group consisting of H, methyl, ethyl, isopropyl, hydroxyl, amino, ethylamino, trifluoromethyl, cyano and halogen; and

- X and Y are independently selected from CH and N.

Just as a few non-limiting examples of pyrimidine analogues, can be named substituted uracils with the formula (B) wherein X is CH, R⁷ is hydroxyl, and R⁸ is methyl, ethyl, isopropyl, amino, ethylamino, trifluoromethyl, cyano, fluoro, chloro, bromo and iodo.

- The term "C₁-C₆ alkyl" as used herein refers to normal, secondary, or tertiary hydrocarbon chains having from 1 to 6 carbon atoms. Examples thereof are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-methyl-1-propyl(i-Bu), 2-butyl (s-Bu) 2-methyl-2-propyl (t-Bu), 1-pentyl (n-pentyl), 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-1-butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl, 3,3-dimethyl-2-butyl, *n*-pentyl, *n*-hexyl.

As used herein and unless otherwise stated, the term " cycloalkyl " means a monocyclic saturated hydrocarbon monovalent radical having from 3 to 6 carbon atoms, such as for instance cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl.

The term " (C₁-C₆) alkoxy " as used herein includes but is not limited to
5 methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy.

As used herein and unless otherwise stated, the term halogen means any atom selected from the group consisting of fluorine (F), chlorine (Cl), bromine (Br) and iodine (I).

10 Any substituent designation that is found in more than one site in a phosphate-modified nucleotide of this invention shall be independently selected.

The term " amino acid " as used herein refers to any " natural amino acid " (Alanine (ala), Arginine (Arg), Asparagine (asn), Aspartic acid (asp), Cysteine (cys), Glutamine (gln), Glutamic acid (glu), Glycine (gly), Histidine (his), Hydroxylysine
15 (Hyl), Hydroxyproline (Hyp), Isoleucine (ile), Leucine (leu), Lysine (lys), Methionine (met), Phenylalanine (phe), Proline (pro), Serine (ser), Threonine (thr), Tryptophan (trp), Tyrosine (tyr), Valine (val)) in D or L conformation (but, within the context of this invention, preferably the L conformation), as well as to " unnatural (or synthetic) amino acids " (e.g., but not limited to, phosphoserine, phosphothreonine,
20 phosphotyrosin, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillarnine, ornithine, citruline, alpha-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). This term also comprises natural and unnatural amino acids being
25 protected at their carboxylic terminus (e.g. as a (C₁-C₆)alkyl, phenyl or benzyl ester or as an amide, such as for example, a mono-(C₁-C₆)alkyl or di-(C₁-C₆)alkyl amide). Other suitable carboxy protecting groups are known to those skilled in the art (See for example, T.W. Greene, Protecting Groups In Organic Synthesis; Wiley: New York, 1981, and references cited therein).

30

It will be appreciated by those skilled in the art that phosphate-modified nucleotides of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some phosphate-modified nucleotides may exhibit polymorphism. It is to be understood that the present invention encompasses
35 any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a phosphate-modified nucleotide of the invention, which possess the

useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase).

- 5 Specific values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents. Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₃-C₆)cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; (C₁-C₆)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; (C₁-C₆)alkanoyl can be acetyl, propanoyl or butanoyl.

- Certain of the phosphate-modified nucleotides herein when substituted with appropriate selected functionalities are capable of acting as prodrugs. These are labile functional groups which separate from an active inhibitory phosphate-modified nucleotide during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, "Design and Application of Prodrugs" in Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). These prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A "prodrug" is thus a covalently modified analog of a therapeutically-active phosphate-modified nucleotide. A prodrug moiety of course can be therapeutically active in its own right.

- Exemplary suitable pro-drug moieties include, but are not limited to, esters of nucleosides like POM (pivaloyloxymethyl), POC (isopropylloxycarbonyloxymethyl) and SATE (S-acyl-2-thioethyl).

- The term "salt" as used herein, refers to the ionic product of a reaction between an acid and a base. Salts of the compounds having structural formula I may be formed at any acid or base functionality within the compound, in particular, R³, R⁴ and R⁵ may represent or comprise an acid or base functionality. In particular, salts of the compounds having structural formula I may be formed as follows. When R³ is H, it is acidic and may therefore engage in salt formation with an anorganic or organic base. R⁴ and R⁵ comprise acid functionalities such as carboxylic groups (i.e. -COOH), which can equally engage in salt formation with an organic or anorganic base. Alternatively, R⁴ and R⁵ may comprise base functionalities such as the

imidazolyl, which in turn can engage in salt formation with an organic or inorganic acid.

The term "prodrug", as used herein, relates to an inactive or significantly less active derivative of a compound having structural formula I as defined herein above or any of its embodiments, which undergoes spontaneous or enzymatic transformation within the body in order to release the pharmacologically active form of the compound. For a comprehensive review, reference is made to Rautio J. et al. ("Prodrugs: design and clinical applications" Nature Reviews Drug Discovery, 2008, doi: 10.1038/nrd2468). In particular for the purpose of the present invention, prodrugs of the compounds having structural formula I may be formed as follows. When R³ is H, a free phosphate acid function is available for prodrug formation as described in detail by Hecker S.J. and Erion M.D. ("Prodrugs of phosphates and phosphonates" Journal of Medicinal Chemistry, 2008, doi: 10.1021/jm701260b). R⁴ and R⁵ comprise acid functionalities such as carboxylic acid groups (i.e. -COOH) which may be used for the formation of a prodrug. Such carboxylic acid prodrug may occur in the form of an ester, in particular acyloxyalkylesters (e.g. pivaloyloxymethyl ester (POM)) or S-acylthioethyl (SATE) esters, a carbonate, a carbamate or an amide, such as amino acid prodrugs.

The term "peptide" as used herein refers to a sequence of 2 to 50 amino acids (e.g. as defined hereinabove) or peptidyl residues. The sequence may be linear or cyclic. Preferably a peptide comprises 2 to 25, or 5 to 20 amino acids.

The term "oligonucleotide" as used herein refers to a polynucleotide formed by a plurality of linked nucleotide units. The nucleotide units each include a nucleoside unit linked together via a phosphate linking group. These nucleotides can be natural or modified in their phosphate, sugar or nucleobase group. The oligonucleotide may be naturally occurring or non naturally occurring.

The term "polymerase" as used herein refers to an enzyme that can synthesize DNA or RNA from a DNA or RNA template and includes but is not limited to Terminator DNA polymerase, KF(exo-)DNA polymerase and HIV Reverse Transcriptase.

BIOLOGICAL APPLICATIONS OF THE INVENTION

Amino acid phosphoramidates, phospho-esters and phospho-thioesters according to this invention may be used as alternative substrates and biotechnology tools.

Fast emerging applications of modified nucleosides as biotechnology tools also require new and efficient ways to synthesize DNA and RNA building blocks such as nucleoside triphosphates and amidites for the use, for example, in PCR, labeling, or enzymatic incorporation of nucleotides, and in the automated DNA synthesis, respectively. Furthermore, some biotechnology applications require incorporation of a nucleotide by enzymatic means using DNA or RNA polymerases. However, at times, due to chemical nature and modifications present in the modified nucleosides, triphosphate synthesis is not always feasible and/or provides insufficient and low yields.

Therefore, an amino acid (e.g. aspartic acid) coupled to a nucleoside monophosphate through a phosphoramidate (P-N) bond can serve as an alternative or substitute group to a pyrophosphate moiety. However, fitting into an active site and the subsequent nucleotidyl transfer may be less efficient for an amino acid phosphoramidate (e.g. Asp-dAMP) compared to the natural substrates/dNTPs (e.g. dATP) for the natural polymerase/enzyme. In this situation, mutated polymerases can be used to increase the efficiency of recognition and incorporation of amino acid phosphoramidate nucleotides. Such an embodiment of the invention with mutated polymerases can be used to specifically select or grow bacteriae by using these amino acid phosphoramidate nucleosides as a substrate. An additional advantage of this application is that polymerases that demonstrated efficient recognition and incorporation of amino acid phosphoramidate nucleosides in our studies are also shown to tolerate various sugar modifications and unnatural nucleobases quite well. Therefore, the enzymatic synthesis of DNA and, RNA sequences containing unnatural nucleobases can be accomplished whilst avoiding at times cumbersome nucleoside triphosphate synthesis and purification.

The amino acid phosphoramidates, phospho-esters and phospho-thioesters of this invention are also useful as antiviral compounds

The compounds of the invention can be employed for the treatment of viral infections, more particularly Human Immunodeficiency Virus (HIV) infections, in particular of Human Immunodeficiency Virus type 1 (HIV-1). When using one or more derivatives of the formula I as defined herein:

- the active ingredients of the compound(s) may be administered to the mammal (including a human being) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization.

- the therapeutically effective amount of the preparation of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is a HIV enzyme inhibiting amount. More preferably, it is a HIV replication inhibiting amount or a HIV enzyme (in particular reverse transcriptase) inhibiting amount of the derivative(s) of formula I as defined herein corresponds to an amount which ensures a plasma level of between 1µg/ml and 100 mg/ml, optionally of 10 mg/ml. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one day intervals.

10 The present invention further relates to a method for preventing or treating a viral infection in a subject or patient by administering to the patient in need thereof a therapeutically effective amount of the compounds of the present invention. The therapeutically effective amount of the compound(s), especially for the treatment of viral infections in humans and other mammals, preferably is a HIV enzyme inhibiting amount. More preferably, it is a HIV replication inhibiting amount or a HIV enzyme (in particular reverse transcriptase) inhibiting amount of the derivative(s) of formula I as defined herein. Depending upon the pathologic condition to be treated and the patient's condition, the said effective amount may be divided into several sub-units per day or may be administered at more than one-day intervals.

20 The present invention also relates to a combination of different antiviral drugs of the invention or to a combination of the antiviral drugs of the invention with other drugs that exhibit anti-HIV.

The invention also relates to a combined preparation of antiviral drugs which may be either:

25 A) a composition comprising

- (a) a combination of two or more of the compounds of the present invention, and
- (b) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

30 for simultaneous, separate or sequential use in the treatment or prevention of a viral infection, or

B) a composition comprising

- (c) one or more anti-viral agents, and
- (d) at least one compound of the present invention, and
- (e) optionally one or more pharmaceutical excipients or pharmaceutically acceptable carriers,

35

for simultaneous, separate or sequential use in the treatment or prevention of a viral infection.

Suitable anti-viral agents (c) for inclusion into the antiviral combined preparations of this invention include for instance, inhibitors of BVDV or HCV replication respectively, such as interferon- α (either pegylated or not), ribavirin and other selective inhibitors of the replication of HCV, such as a compound disclosed in EP1162196, WO 03/010141, WO 03/007945, WO 03/010140 and WO 00/204425 and/or an inhibitor of flaviviral protease and/or one or more additional flavivirus polymerase inhibitors.

The pharmaceutical composition or combined preparation with activity against viral infection according to this invention may contain a compound of the present invention over a broad content range depending on the contemplated use and the expected effect of the preparation. Generally, the content of the compound of the present invention in the combined preparation is within the range of 0.1 to 99.9% by weight, preferably from 1 to 99% by weight, more preferably from 5 to 95% by weight.

When using a pharmaceutical composition of combined preparation:

- the active ingredients may be administered to the mammal (including a human) to be treated by any means well known in the art, i.e. orally, intranasally, subcutaneously, intramuscularly, intradermally, intravenously, intra-arterially, parenterally or by catheterization; and/or
- the therapeutically effective amount of each of the active agents, especially for the treatment of viral infections in humans and other mammals, particularly is a HIV enzyme inhibiting amount.

When applying a combined preparation, the active ingredients may be administered simultaneously but it is also beneficial to administer them separately or sequentially, for instance within a relatively short period of time (e.g. within about 24 hours) in order to achieve their functional fusion in the body to be treated.

The invention also relates to the compounds of the formulae described herein being used for inhibition of the proliferation of other viruses than HIV-1, particularly for the inhibition of other members of the family of the retroviruses.

The present invention further provides veterinary compositions comprising at least one active ingredient as above defined together with a veterinary carrier therefor. Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient.

These veterinary compositions may be administered orally, parenterally or by any other desired route.

More generally, the invention relates to the compounds of formula I being useful as agents having biological activity (particularly antiviral activity) or as
5 diagnostic agents.

The compounds of the invention optionally are bound covalently to an insoluble matrix and used for affinity chromatography separations, depending on the nature of the groups of the compounds, for example compounds with pendant aryl are useful in hydrophobic affinity separations.

10 Those of skill in the art will also recognize that the compounds of the invention may exist in many different protonation states, depending on, among other things, the pH of their environment. While the structural formulae provided herein depict the compounds in only one of several possible protonation states, it will be understood that these structures are illustrative only, and that the invention is not limited to any
15 particular protonation state - any and all protonated forms of the compounds are intended to fall within the scope of the invention.

The term "pharmaceutically acceptable salts" as used herein means the therapeutically active non-toxic salt forms which the compounds of formula I are able to form. Therefore, the compounds of this invention optionally comprise salts of the
20 compounds herein, especially pharmaceutically acceptable non-toxic salts containing, for example, Na⁺, Li⁺, K⁺, Ca²⁺ and Mg²⁺. Such salts may include those derived by combination of appropriate cations such as alkali and alkaline earth metal ions or ammonium and quaternary amino ions with an acid anion moiety, typically a carboxylic acid. The compounds of the invention may bear multiple positive or
25 negative charges. The net charge of the compounds of the invention may be either positive or negative. Any associated counter ions are typically dictated by the synthesis and/or isolation methods by which the compounds are obtained. Typical counter ions include, but are not limited to ammonium, sodium, potassium, lithium, halides, acetate, trifluoroacetate, etc., and mixtures thereof. It will be understood that
30 the identity of any associated counter ion is not a critical feature of the invention, and that the invention encompasses the compounds in association with any type of counter ion. Moreover, as the compounds can exist in a variety of different forms, the invention is intended to encompass not only forms of the compounds that are in association with counter ions (e.g., dry salts), but also forms that are not in
35 association with counter ions (e.g., aqueous or organic solutions). Metal salts typically are prepared by reacting the metal hydroxide with a compound of this

invention. Examples of metal salts which are prepared in this way are salts containing Li^+ , Na^+ , and K^+ . A less soluble metal salt can be precipitated from the solution of a more soluble salt by addition of the suitable metal compound. In addition, salts may be formed from acid addition of certain organic and inorganic acids to basic centers, typically amines, or to acidic groups. Examples of such appropriate acids include, for instance, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, lactic, pyruvic, oxalic (i.e. ethanedioic), malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic (i.e. 2-hydroxybenzoic), p-aminosalicylic and the like. Furthermore, this term also includes the solvates which the compounds of formula I as well as their salts are able to form, such as for example hydrates, alcoholates and the like. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their unionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids, especially the naturally-occurring amino acids found as protein components. The amino acid typically is one bearing a side chain with a basic or acidic group, e.g., lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

The compounds of the invention also include physiologically acceptable salts thereof. Examples of physiologically acceptable salts of the compounds of the invention include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NA_4^+ (wherein A is $\text{C}_1\text{-C}_4$ alkyl). Physiologically acceptable salts of an hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, benzoic, lactic, fumaric, tartaric, maleic, malonic, malic, isethionic, lactobionic and succinic acids; organic sulfonic acids, such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids; and inorganic acids, such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound containing a hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ and NA_4^+ (wherein A typically is independently selected from H or a $\text{C}_1\text{-C}_4$ alkyl group). However, salts of acids or bases which are not physiologically acceptable may also find use, for example, in the preparation or

purification of a physiologically acceptable compound. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

As used herein and unless otherwise stated, the term "enantiomer" means
5 each individual optically active form of a compound of the invention, having an optical purity or enantiomeric excess (as determined by methods standard in the art) of at least 80% (i.e. at least 90% of one enantiomer and at most 10% of the other enantiomer), preferably at least 90% and more preferably at least 98%.

The term "isomers" as used herein means all possible isomeric forms,
10 including tautomeric and stereochemical forms, which the compounds of formula I may possess, but not including position isomers. Typically, the structures shown herein exemplify only one tautomeric or resonance form of the compounds, but the corresponding alternative configurations are contemplated as well. Unless otherwise stated, the chemical designation of compounds denotes the mixture of all possible
15 stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers (since the compounds of formula I may have at least one chiral center) of the basic molecular structure, as well as the stereochemically pure or enriched compounds. More particularly, stereogenic centers may have either the R- or S-configuration, and multiple bonds may have either cis- or trans-configuration. Pure
20 isomeric forms of the said compounds are defined as isomers substantially free of other enantiomeric or diastereomeric forms of the same basic molecular structure. In particular, the term "stereoisomerically pure" or "chirally pure" relates to compounds having a stereoisomeric excess of at least about 80% (i.e. at least 90% of one isomer and at most 10% of the other possible isomers), preferably at least 90%, more
25 preferably at least 94% and most preferably at least 97%. The terms "enantiomerically pure" and "diastereomerically pure" should be understood in a similar way, having regard to the enantiomeric excess, respectively the diastereomeric excess, of the mixture in question. Separation of stereoisomers is accomplished by standard methods known to those in the art. One enantiomer of a
30 compound of the invention can be separated substantially free of its opposing enantiomer by a method such as formation of diastereomers using optically active resolving agents ("Stereochemistry of Carbon Compounds," (1962) by E. L. Eliel, McGraw Hill; Lochmuller, C. H., (1975) J. Chromatogr., 113:(3) 283-302). Separation of isomers in a mixture can be accomplished by any suitable method, including: (1)
35 formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds

with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure enantiomers, or (3) enantiomers can be separated directly under chiral conditions. Under method (1), diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-b-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid, or lactic acid can result in formation of the diastereomeric salts. Alternatively, by method (2), the substrate to be resolved may be reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S. (1994) Stereochemistry of Organic Compounds, John Wiley & Sons, Inc., p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the free, enantiomerically enriched xanthene. A method of determining optical purity involves making chiral esters, such as a menthyl ester or Mosher ester, a-methoxy-a-(trifluoromethyl)phenyl acetate (Jacob III. (1982) J. Org. Chem. 47:4165), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric diastereomers. Stable diastereomers can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (Hoye, T., WO96/15111). Under method (3), a racemic mixture of two asymmetric enantiomers is separated by chromatography using a chiral stationary phase. Suitable chiral stationary phases are, for example, polysaccharides, in particular cellulose or amylose derivatives. Commercially available polysaccharide based chiral stationary phases are ChiralCel™ CA, OA, OB5, OC5, OD, OF, OG, OJ and OK, and Chiralpak™ AD, AS, OP(+) and OT(+). Appropriate eluents or mobile phases for use in combination with said polysaccharide chiral stationary phases are hexane and the like, modified with an alcohol such as ethanol, isopropanol and the like.

The terms cis and trans are used herein in accordance with Chemical Abstracts nomenclature and include reference to the position of the substituents on a ring moiety. The absolute stereochemical configuration of the compounds of formula I may easily be determined by those skilled in the art while using well-known methods such as, for example, X-ray diffraction.

The compounds of the invention may be formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral
5 administration generally will be isotonic. Formulations optionally contain excipients such as those set forth in the "Handbook of Pharmaceutical Excipients" (1986) and include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like.

10 Subsequently, the term "pharmaceutically acceptable carrier" as used herein means any material or substance with which the active ingredient is formulated in order to facilitate its application or dissemination to the locus to be treated, for instance by dissolving, dispersing or diffusing the said composition, and/or to facilitate its storage, transport or handling without impairing its effectiveness. The
15 pharmaceutically acceptable carrier may be a solid or a liquid or a gas which has been compressed to form a liquid, i.e. the compositions of this invention can suitably be used as concentrates, emulsions, solutions, granulates, dusts, sprays, aerosols, suspensions, ointments, creams, tablets, pellets or powders.

Suitable pharmaceutical carriers for use in the said pharmaceutical
20 compositions and their formulation are well known to those skilled in the art, and there is no particular restriction to their selection within the present invention. They may also include additives such as wetting agents, dispersing agents, stickers, adhesives, emulsifying agents, solvents, coatings, antibacterial and antifungal agents (for example phenol, sorbic acid, chlorobutanol), isotonic agents (such as sugars or
25 sodium chloride) and the like, provided the same are consistent with pharmaceutical practice, i.e. carriers and additives which do not create permanent damage to mammals. The pharmaceutical compositions of the present invention may be prepared in any known manner, for instance by homogeneously mixing, coating and/or grinding the active ingredients, in a one-step or multi-steps procedure, with the
30 selected carrier material and, where appropriate, the other additives such as surface-active agents. They may also be prepared by micronisation, for instance in view to obtain them in the form of microspheres usually having a diameter of about 1 to 10 μm , namely for the manufacture of microcapsules for controlled or sustained release of the active ingredients.

35 Suitable surface-active agents, also known as emulgent or emulsifier, to be used in the pharmaceutical compositions of the present invention are non-ionic,

cationic and/or anionic materials having good emulsifying, dispersing and/or wetting properties. Suitable anionic surfactants include both water-soluble soaps and water-soluble synthetic surface-active agents. Suitable soaps are alkaline or alkaline-earth metal salts, unsubstituted or substituted ammonium salts of higher fatty acids (C₁₀-C₂₂), e.g. the sodium or potassium salts of oleic or stearic acid, or of natural fatty acid mixtures obtainable from coconut oil or tallow oil. Synthetic surfactants include sodium or calcium salts of polyacrylic acids; fatty sulphonates and sulphates; sulphonated benzimidazole derivatives and alkylarylsulphonates. Fatty sulphonates or sulphates are usually in the form of alkaline or alkaline-earth metal salts, unsubstituted ammonium salts or ammonium salts substituted with an alkyl or acyl radical having from 8 to 22 carbon atoms, e.g. the sodium or calcium salt of lignosulphonic acid or dodecylsulphonic acid or a mixture of fatty alcohol sulphates obtained from natural fatty acids, alkaline or alkaline-earth metal salts of sulphuric or sulphonic acid esters (such as sodium lauryl sulphate) and sulphonic acids of fatty alcohol/ethylene oxide adducts. Suitable sulphonated benzimidazole derivatives preferably contain 8 to 22 carbon atoms. Examples of alkylarylsulphonates are the sodium, calcium or alcanolamine salts of dodecylbenzene sulphonic acid or dibutyl-naphtalenesulphonic acid or a naphtalene-sulphonic acid/formaldehyde condensation product. Also suitable are the corresponding phosphates, e.g. salts of phosphoric acid ester and an adduct of p-nonylphenol with ethylene and/or propylene oxide, or phospholipids. Suitable phospholipids for this purpose are the natural (originating from animal or plant cells) or synthetic phospholipids of the cephalin or lecithin type such as e.g. phosphatidylethanolamine, phosphatidylserine, phosphatidylglycerine, lysolecithin, cardiolipin, dioctanylphosphatidyl-choline, dipalmitoylphosphatidyl - choline and their mixtures.

Suitable non-ionic surfactants include polyethoxylated and polypropoxylated derivatives of alkylphenols, fatty alcohols, fatty acids, aliphatic amines or amides containing at least 12 carbon atoms in the molecule, alkylarenesulphonates and dialkylsulphosuccinates, such as polyglycol ether derivatives of aliphatic and cycloaliphatic alcohols, saturated and unsaturated fatty acids and alkylphenols, said derivatives preferably containing 3 to 10 glycol ether groups and 8 to 20 carbon atoms in the (aliphatic) hydrocarbon moiety and 6 to 18 carbon atoms in the alkyl moiety of the alkylphenol. Further suitable non-ionic surfactants are water-soluble adducts of polyethylene oxide with polypropylene glycol, ethylenediamino-polypropylene glycol containing 1 to 10 carbon atoms in the alkyl chain, which adducts contain 20 to 250 ethyleneglycol ether groups and/or 10 to 100

propyleneglycol ether groups. Such compounds usually contain from 1 to 5 ethyleneglycol units per propyleneglycol unit. Representative examples of non-ionic surfactants are nonylphenol -polyethoxyethanol, castor oil polyglycolic ethers, polypropylene/polyethylene oxide adducts, tributylphenoxyethoxyethanol, 5 polyethyleneglycol and octylphenoxyethoxyethanol. Fatty acid esters of polyethylene sorbitan (such as polyoxyethylene sorbitan trioleate), glycerol, sorbitan, sucrose and pentaerythritol are also suitable non-ionic surfactants.

Suitable cationic surfactants include quaternary ammonium salts, particularly halides, having 4 hydrocarbon radicals optionally substituted with halo, phenyl, 10 substituted phenyl or hydroxy; for instance quaternary ammonium salts containing as N-substituent at least one C8C22 alkyl radical (e.g. cetyl, lauryl, palmityl, myristyl, oleyl and the like) and, as further substituents, unsubstituted or halogenated lower alkyl, benzyl and/or hydroxy-lower alkyl radicals.

A more detailed description of surface-active agents suitable for this purpose 15 may be found for instance in "McCutcheon's Detergents and Emulsifiers Annual" (MC Publishing Corp., Ridgewood, New Jersey, 1981), "Tensid-Taschenbuch", 2 d ed. (Hanser Verlag, Vienna, 1981) and "Encyclopaedia of Surfactants" (Chemical Publishing Co., New York, 1981).

Compounds of the invention and their physiologically acceptable salts 20 (hereafter collectively referred to as the active ingredients) may be administered by any route appropriate to the condition to be treated, suitable routes including oral, rectal, nasal, topical (including ocular, buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural). The preferred route of administration may vary with for example the 25 condition of the recipient.

While it is possible for the active ingredients to be administered alone it is preferable to present them as pharmaceutical formulations. The formulations, both for veterinary and for human use, of the present invention comprise at least one active ingredient, as above described, together with one or more pharmaceutically 30 acceptable carriers therefore and optionally other therapeutic ingredients. The carrier(s) optimally are "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The formulations include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, 35 intravenous, intradermal, intrathecal and epidural) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any of

the methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or
5 finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water
10 liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or
15 granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. For infections of
20 the eye or other external tissues e.g. mouth and skin, the formulations are optionally applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When
25 formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, i.e. an alcohol having two or more hydroxyl groups such as propylene glycol,
30 butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethylsulfoxide and related analogs.

35 The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an

emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Optionally, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus the cream should optionally be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is optionally present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w. Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate. Formulations suitable for nasal administration wherein the carrier is a solid include a coarse powder having a particle size for example in the range 20 to 500 microns (including particle sizes in a range between 20 and 500 microns in increments of 5 microns such as 30 microns, 35 microns, etc), which is administered in the manner in which snuff is taken, i.e. by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a

liquid, for administration as for example a nasal spray or as nasal drops, include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

5 Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

10 Formulations suitable for parenteral administration include aqueous and non-
aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and
15 vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

20 Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

25 It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

30 This invention includes controlled release pharmaceutical formulations containing as active ingredient one or more compounds of the invention ("controlled release formulations") in which the release of the active ingredient can be controlled and regulated to allow less frequency dosing or to improve the pharmacokinetic or toxicity profile of a given invention compound. Controlled release formulations adapted for oral administration in which discrete units comprising one or more compounds of the invention can be prepared according to conventional methods.

35 Additional ingredients may be included in order to control the duration of action of the active ingredient in the composition. Control release compositions may thus be achieved by selecting appropriate polymer carriers such as for example polyesters, polyamino acids, polyvinyl pyrrolidone, ethylene-vinyl acetate copolymers,

methylcellulose, carboxymethylcellulose, protamine sulfate and the like. The rate of drug release and duration of action may also be controlled by incorporating the active ingredient into particles, e.g. microcapsules, of a polymeric substance such as hydrogels, polylactic acid, hydroxymethylcellulose, polyniethyl methacrylate and the other above-described polymers. Such methods include colloid drug delivery systems like liposomes, microspheres, microemulsions, nanoparticles, nanocapsules and so on. Depending on the route of administration, the pharmaceutical composition may require protective coatings. Pharmaceutical forms suitable for injectionable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation thereof. Typical carriers for this purpose therefore include biocompatible aqueous buffers, ethanol, glycerol, propylene glycol, polyethylene glycol and the like and mixtures thereof.

In view of the fact that, when several active ingredients are used in combination, they do not necessarily bring out their joint therapeutic effect directly at the same time in the mammal to be treated, the corresponding composition may also be in the form of a medical kit or package containing the two ingredients in separate but adjacent repositories or compartments. In the latter context, each active ingredient may therefore be formulated in a way suitable for an administration route different from that of the other ingredient, e.g. one of them may be in the form of an oral or parenteral formulation whereas the other is in the form of an ampoule for intravenous injection or an aerosol.

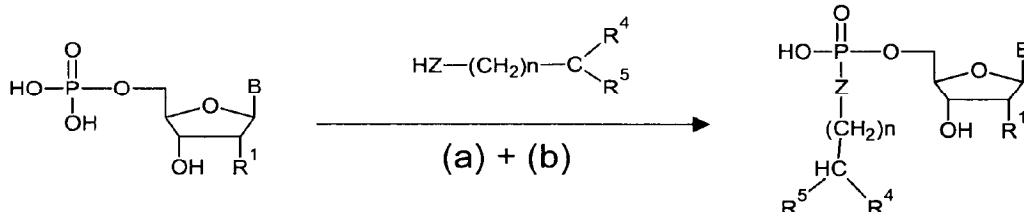
The presented invention shows that a phosphate-modified nucleoside such as 2'-deoxy-adenine-5'-aspartyl-phosphoramidate is successfully recognized and efficiently incorporated into a growing DNA strand by HIV RT and Terminator DNA polymerase. This means that an aspartyl-phosphoramidate moiety can mimic a pyrophosphate group and behave as a good leaving group in a nucleotidyl transfer. Incorporation of phosphoramidate analogues, although to a lesser extent, was also observed for histidyl and glycyl phosphoramidates, respectively. Therefore, it is feasible to use chain-terminating nucleotides coupled to aspartic acid through a phosphoramidate linkage for a direct inhibition of HIV RT or other viral polymerases as depicted in Figure 2A. Effective inhibition of HIV RT or other viral polymerases by a modified nucleoside requires its activation by cellular nucleoside kinases and conversion into a corresponding nucleoside triphosphate. Administration of AZT phosphoramidate **9** as a substitute for AZT nucleoside triphosphate can therefore eliminate a requirement for kinase activation. However, it is important to assess the ability of HIV RT to recognize and insert AZT phosphoramidate **9** with satisfactory

efficiency. A potential drawback of this approach could be the charged nature of aspartyl phosphoramidate nucleotides. As a charged molecule, the aspartyl phosphoramidate of AZT is not likely to pass through a cellular membrane unless active transport is involved. However, intracellular diffusion is likely facilitated by masking the negative charges of carboxylate moieties by means of esterification as shown in Figure 2B. Once a protected amino acid phosphoramidate analogue is in the cytosol, it can be transformed back to a charged, acidic form through the action of cellular esterases. These principles of monophosphate activation and subsequent inhibition of viral polymerases, as shown in figure 2A and 2B for AZT, equally apply to other chain-terminating nucleotides known in the art.

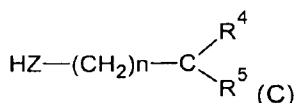
MANUFACTURE OF THE COMPOUNDS OF THE INVENTION

The synthesis of amino acid phosphoramidate nucleotide analogues of this invention may be accomplished according to the method illustrated by scheme 2, starting from a nucleoside monophosphate, which itself can be tailor-made by phosphorylation of a suitable nucleoside.

Scheme 2



The compounds according to the invention may be synthesized by derivatisation of the 5'-mono-phosphate nucleoside precursor molecule as illustrated in Scheme 2. In a first step (a), the phosphate group of the 5'-mono-phosphate nucleoside is coupled with the Z-group of the reagent having structural formula (C)

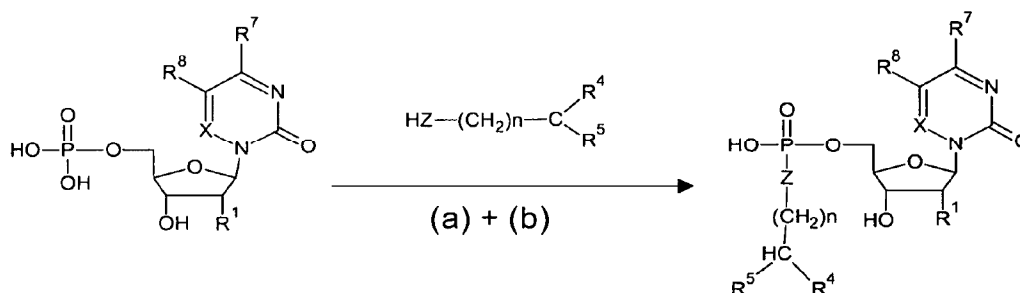


wherein Z, R⁴ and R⁵ are the same as defined for formula I and III. Said coupling reaction results in the formation of a phosphate ester (when Z = O), phosphate amide (when Z = NH or N-R) or phosphate thioester (when Z = S). Said coupling reaction may be performed using any coupling agent (also referred to as dehydrating agent) known in the art for esterification or amide formation, in particular using a carbodiimide coupling agent, more in particular using dicyclohexylcarbodiimide (DCC). The coupling reaction is performed at a temperature between room

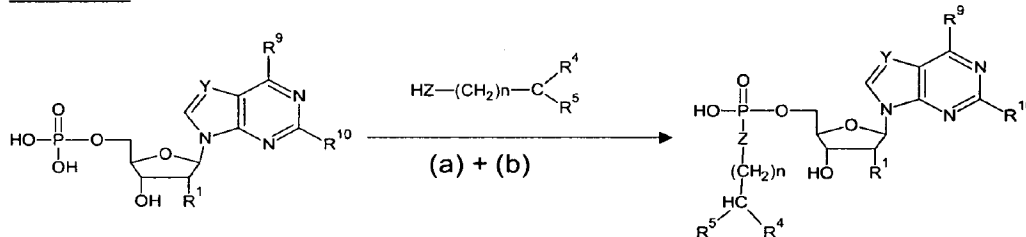
temperature and reflux temperature of the solvent the reaction is performed in. depending on the nature of R⁴ and R⁵, additional acid, hydroxy or amine functionalities in reagent (C) may be transiently protected to prevent these functionalities from interfering with the condensation reaction between the phosphate acid and Z. Therefore, the synthetic route provides for an optional subsequent step of deprotecting such functionalities.

Schemes 3 and 4 below illustrate a synthetic route for the synthesis of pyrimidine and purine derived compounds according to the present invention respectively.

Scheme 3



Scheme 4



Alternatively, the compounds according to the structural formula I, or any specific embodiments thereof, may be obtained using a synthetic procedure as illustrated by scheme 1 herein above.

EXAMPLES

EXAMPLE 1: SYNTHESIS

Scheme 5 depicts 16 specific phosphate-modified nucleotides, but is applicable to other phosphate-modified nucleotides disclosed in this invention by introducing other substituents for R¹ and R² (i.e. using other alkyl residues in stead of Methyl). L-amino

acids were used for synthesis of all phosphoramidate analogues of the examples wherein said amino acid is coupled to the phosphor atom with its α -amino function. However, this procedure is applicable to all D- and L-amino acids (both natural and unnatural) and organic phosphate-modified nucleotides that contain an amino group.

- 5 The deprotection of the amino acid moiety was carried out with 0.4 M sodium hydroxide in methanol-water solution. For the isolation of the pure analogue phosphate-modified nucleotides, silica gel column chromatography was employed with i PrOH-NH₃-H₂O mixture as an elution system. A series of phosphoramidate analogs coupled to a variety of natural L-amino acids synthesized as examples in this
- 10 study is shown in Scheme 5, and Figure 1. Step a of the synthesis illustrated by scheme 5 was performed with the use of DCC as coupling agent in a mixture of water and *tert*-butanol under reflux temperature. Step b illustrated the optional saponification using 0.4M NaOH in a mixture of water and methanol.

15 Scheme 5
EMBED

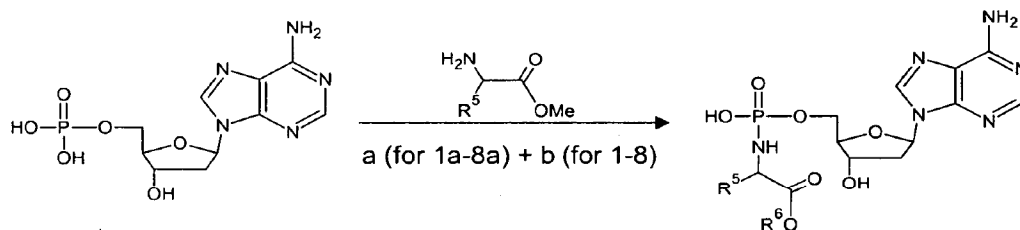


Table 1

	R ⁶	R ⁵		R ⁶	R ⁵
1	H	-CH ₂ -COOH	1a	CH ₃	-CH ₂ -COOH
2	H	-CH ₂ -CH ₂ -COOH	2a	CH ₃	-CH ₂ -CH ₂ -COOH
3	H	-H	3a	CH ₃	-H
4	H	-CH ₃	4a	CH ₃	-CH ₃
5	H	-CH ₂ -Ph-OH	5a	CH ₃	-CH ₂ -Ph-OH
6	H		6a	CH ₃	
7	H	-CH ₂ -OH	7a	CH ₃	-CH ₂ -OH
8	H		8a	CH ₃	

Typical experimental procedure for synthesis of 5'-amino acid phosphoramidates of 2'-deoxyadenine. This procedure is however generally applicable to other phosphoramidates of the invention.

5 Synthesis of 2'-deoxy-adenosine-5'-dimethylaspartyl-phosphoramidate (1a)

- In a two neck flask, 2'-deoxyadenosine-5'-monophosphoric acid hydrate (200 mg, 0.572 mmoles) and L-aspartic acid dimethyl ester hydrochloride (791 mg, 4 mmoles, 7 equiv.) were dissolved in a mixture of *tert*-butanol (9 ml) and H₂O (2ml). A few drops of triethylamine (Et₃N) were added to the solution to facilitate dissolution.
- 10 An appropriate amount of N,N'-dicyclohexylcarbodiimide (DCC) (826 mg, 4 mmoles, 7 equiv.) was dissolved under argon in 1 ml of *tert*-butanol and was dropwise added to the reaction mixture. The reaction mixture was refluxed carefully for 3-4 hours while stirring under argon. The progress of the reaction was monitored by TLC (*i*PrOH:NH₃:H₂O). Upon completion, the reaction mixture was cooled down and the
- 15 solvent was removed by rotary evaporation. The product was isolated by silica column chromatography eluting with CHCl₃:MeOH:H₂O gradient affording the product as a white solid (238 mg, 87.8% yield) that was characterised as follows:
- ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.42 (s, 1H), 8.14 (s, 1H), 7.30 (s, 2H *NH*₂), 6.36 (t, *J* = 7.0, 1H, H1'), 4.44 (s, 1H, H3'), 4.06-3.87 (m, 2H, H4', CHCOOCH₃), 3.81-3.69 (m, 2H, H5'), 3.57 (s, 3H, CHCOOCH₃), 3.55 (s, 3H, CH₂COOCH₃), 2.79-2.58 (m, 3H, H2', CH₂), and 2.35-2.19 (m, 1H, H2') ppm;
 - ¹³C (500 MHz, DMSO-*d*₆): δ 174.04 (d, *J*(C,P) = 25), 171.59 (d, *J*(C,P) = 15.0), 156.46, 153.09, 149.71, 139.80, 119.31, 86.81 (d, *J*(C,P) = 30.0), 83.51, 71.83, 64.61, 52.26, 51.84, 50.71, 39.08, and 35.88 ppm;
 - 25 - ³¹P NMR (300 MHz, H₂O): δ 5.73;
 - MS (ESI): [M-H] = 473.4 High res. MS (ESI): *m/z* calculated for C₁₆H₂₃N₆O₉P 475.1324, actual 475.1333.

Synthesis of 2'-deoxy-adenosine-5'-aspartyl-phosphoramidate (1)

- 30 A solution (4-5 ml) of 0.4 M NaOH (MeOH:H₂O 4:1) was added to 2'-deoxy-adenine-5'-dimethoxyaspartyl phosphoramidate (238 mg, 0.507 mmoles) and a deprotection reaction was carried out at room temperature while stirring under argon for 2-4 hours. The course of the reaction was monitored by TLC (*i*PrOH:NH₃:H₂O) until the disappearance of the starting material. Once the starting material has
- 35 disappeared, the reaction mixture was neutralized by addition of 2M TEAA. The solvent was removed under reduced pressure and the resulting residue was dried by

lyophilization. The desired product was purified by silica column chromatography eluting with *i*PrOH:NH₃:H₂O gradient. The product was isolated and concentrated by lyophilization to provide a white solid (137 mg, 61.1%) that was characterised as follows:

- 5 - ¹H NMR (300 MHz, D₂O): δ 8.39 (s, 1H), 8.15 (s, 1H), 6.39 (t, *J* = 7.2, 1H, H1'), 4.61 (dd, *J* = 8.7, 5.7, 1H, H3'), 4.16 (s, 1H, CHCOOCH₃), 3.99-3.76 (m, 2H, H5'), 3.75-3.605 (m, 1H, H4'), 2.80-2.64 (m, 1H, H2'), and 2.56-2.30 (m, 3H, H2', CH₂) ppm;
- ¹³C (300 MHz, D₂O): δ 177.50, 174.14, 155.33, 152.40, 148.38, 139.38, 86.11 (d, *J*(C,P) = 39.0), 83.66 (d, *J*(C,P) = 18.0), 71.32 (d, *J*(C,P) = 9.0), 63.98 (d, *J*(C,P) = 21.0), 52.19, 39.13 (d, *J*(C,P) = 30), and 36.48 ppm;
- 10 - ³¹P NMR (300 MHz, D₂O): δ 6.71;
- MS (ESI): [M-H] = 445.1 High res. MS (ESI): *m/z* calculated for C₁₄H₁₉N₆O₉P 445.0872, actual 445.0864.

15

Amino acid phosphoramidates **2-8** and **2a-8a** were synthesized similarly to **1** and **1a** using the same experimental procedure:

- 2'-deoxy-adenosine-5'-dimethylglutamyl-phosphoramidate (2a) (MW = 488.39, C₁₇H₂₅N₆O₉P, yield 80.2%) was characterised as follows:
- 20 - ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.39 (s, 1H), 8.13 (s, 1H), 7.287 (s, 2H NH₂), 6.34 (t, *J* = 6.9, 1H, H1'), 4.41 (s, 1H, H3'), 3.92 (s, 1H, CHCOOCH₃), 3.73-3.66 (m, 3H, H4', H5'), 3.55 (s, 3H, CHCOOCH₃), 3.52 (s, 3H, CH₂COOCH₃), 2.77-2.60 (m, 1H, H2'), 2.42-2.18 (m, 3H, H2', CH₂), and 1.93-1.58 (m, 2H, CH₂) ppm;
 - 25 - ¹³C (300 MHz, D₂O) δ 176.38 (d, *J* = 15), 175.74, 155.38, 152.56, 148.59, 140.27, 139.75, 118.50, 85.96 (*J*(C,P) = 36.0), 83.60, 71.72, 63.89 (d, *J*(C,P) = 21.0), 53.88, 52.52, 52.05, 38.85, 29.66, and 28.46 (d, *J*(C,P) = 27);
 - ³¹P NMR (300 MHz, D₂O): δ 6.19; and
 - MS (ESI): [M+Na] = 459.5 High res. MS (ESI): *m/z* calculated for C₁₇H₂₅N₆O₉P 487.1342 [M-H], actual 487.1319.

30

2'-deoxy-adenosine-5'-glutamyl-phosphoramidate (2) (MW = 460.33, C₁₅H₂₁N₆O₉P, yield 61%) was characterised as follows:

- 35 - ¹H NMR (300 MHz, D₂O): δ 8.39 (s, 1H), 8.13 (s, 1H), 6.40 (t, *J* = 6.9, 1H, H1'), 4.58 (s, 1H, H3'), 4.15 (s, 1H, CHCOOCH₃), 3.94-3.76 (m, 2H, H5'), 3.47-3.33 (m,

- 1H, H4'), 2.78-2.61 (m, 1H, H2'), 2.55-2.41 (m, 1H, H2'), 2.17-2.03 (m, 2H, CH₂), and 1.85-1.61 (m, 2H, CH₂) ppm;
- ³¹P NMR (300 MHz, D₂O): δ 7.17;
 - ¹³C (500 MHz, D₂O) δ 182.88, 181.57, 155.34, 152.50, 148.49, 140.27, 139.77,
 - 5 118.38, 86.06, 83.56 (d, J(C,P) = 40), 71.39, 63.93, 56.71, 39.15, 33.76, and 31.90 ppm;
 - MS (ESI): [M-H] = 459.1 High res. MS (ESI): m/z calculated for C₁₅H₂₁N₆O₉P 459.1029 [M-H], actual 459.1029.
- 10 2'-deoxy-adenosine-5'-methylglycidyl-phosphoramidate (3a) (MW = 402.29, C₁₃H₁₉N₆O₇P, yield 69.8%) was characterised as follows:
- ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.41 (s, 1H), 8.13 (s, 1H), 7.25 (s, 2H, NH₂), 6.34 (t, J = 6.6), 4.44 (s, 1H, H3'), 3.98-3.88 (m, 1H, H4'), 3.82-3.69 (m, 2H, H5'), 3.55 (s, 3H, CHCOOCH₃), 3.50 (d, J 3, 2H, CH₂), 2.77-2.61 (m, 1H, H2'), and
 - 15 2.34-2.17 (m, 1H, H2') ppm;
 - ³¹P NMR (300 MHz, DMSO-*d*₆): δ 4.44 ppm; and
 - MS (ESI): [M-H] = 401.1 High res. MS (ESI): m/z calculated for C₁₃H₁₉N₆O₇P 401.0974 [M-H], actual 401.0987.
- 20 2'-deoxy-adenosine-5'-glycidyl-phosphoramidate (3) (MW = 388.27, C₁₂H₁₇N₆O₇P, yield 22.2%) was characterised as follows:
- ¹H NMR (300 MHz, D₂O): δ 8.29 (s, 1H), 8.02 (s, 1H), 6.32 (br s, 1H, H1'), 4.58 (s, 1H, H3'), 4.15 (s, 1H, H4'), 3.87 (s, 2H, H5'), 3.24 (d, J = 8.4, 2H, CH₂), 2.80-2.60 (m, 1H, H2'), and 2.57-2.38 (m, 1H, H2') ppm;
 - 25 - ³¹P NMR (300 MHz, D₂O): δ 8.15 ppm;
 - MS (ESI): [M-H] = 387.1 High res. MS (ESI): m/z calculated for C₁₂H₁₇N₆O₇P 387.0818 actual 387.0810.
- 2'-deoxy-adenosine-5'-methylalanyl-phosphoramidate (4a) (MW = 416.32, C₁₄H₂₁N₆O₇P, yield 94.2%) was characterised as follows:
- ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.41 (s, 1H), 8.13 (s, 1H), 7.26 (s, 2H, NH₂), 6.35 (t, J = 6.6, 1H, H1'), 4.44 (t, J = 2.7, 1H, H3'), 3.98-3.88 (m, 1H, H4'), 3.83-3.69 (m, 3H, H5', CHCOOH), 3.51 (s, 3H, CHCOOCH₃), 2.77-2.61 (m, 1H, H2'), 2.34-2.20 (m, 1H, H2'), and 1.14 (d, J = 1.9, 3H, CH₃) ppm;
 - 35 - ³¹P NMR (300 MHz, DMSO-*d*₆): δ 3.37; and

- MS (ESI): [M-H] = 415.1 High res. MS (ESI): m/z calculated for $C_{14}H_{21}N_6O_7P$ 415.1131 actual 415.1143.

2'-deoxy-adenosine-5'-alanyl-phosphoramidate (4) (MW = 402.29, $C_{13}H_{19}N_6O_7P$, yield

5 94.9%) was characterised as follows:

- ^1H NMR (300 MHz, DMSO- d_6): δ 8.44 (s, 1H), 8.13 (s, 1H), 7.29 (br s, 2H, NH_2), 6.35 (t, J = 6.7, 1H, $H1'$), 4.45 (s, 1H, $H3'$), 3.96 (s, 1H, $H4'$), 3.43-3.25 (m, 2H, $H5'$), 3.45-3.25 (m, 1H, $CHCOOH$), 2.78-2.60 (m, 1H, $H2'$), 2.35-2.19 (m, 1H, $H2'$), and 1.08 (d, J = 6.8, 3H, CH_3) ppm;
- 10 - ^{31}P NMR (300 MHz, D_2O): δ 8.15; and
- MS (ESI): [M-H] = 401.1 High res. MS (ESI): m/z calculated for $C_{13}H_{19}N_6O_7P$ 401.0974 actual 401.0957.

2'-deoxy-adenosine-5'-methyltyrosinyl-phosphoramidate (5a) (MW = 508.42,

15 $C_{20}H_{25}N_6O_8P$, yield 45%) was characterised as follows:

- ^1H NMR (300 MHz, DMSO- d_6): δ 9.46 (s, 1H, OH), 8.42 (s, 1H), 8.12 (s, 1H), 7.27 (s, 2H, NH_2), 6.87 (d, J = 8.4, 2H, Ar), 6.61 (d, J = 8.1, 2H, Ar), 6.34 (t, J = 6.9, 1H, $H1'$), 5.74 (br s, 1H, 3'-OH), 4.39 (s, 1H, $H3'$), 3.97-3.75 (m, 2H, $H4'$, $CHCOOCH_3$), 3.74-3.59 (m, 2H, $H5'$), 3.45 (s, 3H, $CHCOOCH_3$), 2.82-2.60 (m, 20 3H, $H2'$, CH_2), and 2.32-2.18 (m, 1H, $H2'$) ppm;
- ^{13}C (300 MHz, D_2O) δ 176.53 (d, $J(C,P)$ = 18), 155.39, 154.01, 152.52, 148.58, 139.63, 130.20, 128.38, 114.94, 85.88 ($J(C,P)$ = 36.0), 83.49, 71.15, 63.78, 56.28, 52.31, 38.92, 38.87, 38.87;
- ^{31}P NMR (300 MHz, DMSO): δ 3.09; and
- 25 - MS (ESI): [M+H] = 509.1 High res. MS (ESI): m/z calculated for $C_{20}H_{25}N_6O_8P$ 509.1549 actual 509.1547.

2'-deoxy-adenosine-5'-tyrosinyl-phosphoramidate (5) (MW = 494.39, $C_{19}H_{23}N_6O_8P$, yield 92.1%) was characterised as follows:

- 30 ^1H NMR (300 MHz, DMSO- d_6): δ 8.42 (s, 1H), 8.13 (s, 1H), 7.27 (s, 2H, NH_2), 6.94 (d, J = 8.4, 2H, Ar), 6.56 (d, J = 8.4, 2H, Ar), 6.33 (t, J = 6.3, 1H, $H1'$), 5.41 (br s, 1H, 3'-OH), 4.36-4.26 (m, 1H, $H3'$), 3.83-3.74 (m, 1H, $H4'$), 3.57-3.56 (m, 2H, $H5'$), 3.19-3.05 (m, 1H, $CHCOOH$), 3.45 (s, 3H, $CHCOOCH_3$), 2.45 (d, J = 8.3, CH_2), 2.60-2.52 (m, 1H, $H2'$), 2.28-2.18 (m, 1H, $H2'$).
- 35 ^{31}P NMR (300 MHz, D_2O): δ 6.23

MS (ESI): [M-H] = 493.2 High res. MS (ESI): m/z calculated for C₁₉H₂₃N₈O₈P 493.1237 actual 493.1212.

2'-deoxy-adenosine-5'-methylhistidyl-phosphoramidate (6a) (MW = 482.39,

5 C₁₇H₂₃N₈O₇P, yield 49.5%) was characterised as follows:

¹H NMR (300 MHz, DMSO-*d*₆): δ 8.40 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.26 (s, 2H, NH₂), 7.05 (s, 1H), 6.35 (t, *J* = 6.6, 1H, H1'), 4.41 (t, *J* = 2.7, 1H, H3'), 3.94-3.92 (s, 1H, CHCOOCH₃), 3.83-3.65 (m, 2H, CH₂), 3.53 (s, 3H, COOCH₃), 2.89 (ddd, *J* = 5.1, 15.0, 33.0, 2H, H5'), 2.75-2.61 (m, 1H, H2'), 2.33-2.19 (m, 1H, H2').

10 ³¹P NMR (300 MHz, DMSO-*d*₆): δ 3.77

MS (ESI): [M+H] = 483.0

2'-deoxy-adenosine-5'-histidyl-phosphoramidate (6) (MW = 468.36, C₁₆H₂₁N₈O₇P, yield 72.9%) was characterised as follows:

15 ¹H NMR (300 MHz, D₂O): δ 8.30 (d, 1H, *J* = 1.5), 8.29 (s, 1H), 8.03 (s, 1H), 6.95 (s, 1H), 6.33 (t, *J* = 6.9, 1H, H1'), 4.57 (dt, *J* = 3.3, 6.3, 1H, H3'), 4.14 (s, 1H, H3'), 3.94-3.78 (m, 2H, H5'), 3.71-3.59 (m, 1H, CHCOOH), 2.85-2.64 (m, 3H, H2', CH₂), 2.55-2.42 (m, 1H, H2').

¹³C (600 MHz, DMSO-*d*₆): δ 178.29 (d, *J*(C,P) = 33.7), 155.02, 152.32, 148.42, 20 139.55, 132.34, 129.21, 118.14, 116.12, 85.67 (d, *J*(C,P) = 36.4), 83.26, 70.93, 63.59 (d, *J*(C,P) = 19.3), 55.86, 38.32, 29.34 (d, *J*(C,P) = 11.2), 23.52.

³¹P NMR (300 MHz, D₂O): δ 6.44

MS (ESI): [M-H] = 467.1 High res. MS (ESI): m/z calculated for C₁₆H₂₁N₈O₇P 467.1193 actual 467.1191.

25

2'-deoxy-adenosine-5'-methylserinyl-phosphoramidate (7a) (MW = 432.32,

C₁₄H₂₁N₆O₈P, yield 77.8%) was characterised as follows:

¹H NMR (300 MHz, DMSO-*d*₆): δ 8.41 (s, 1H), 8.14 (s, 1H), 7.26 (s, 2H NH₂), 6.35 (t, *J* = 6.6, 1H, H1'), 4.50-4.39 (m, 1H, H3'), 4.00-3.89 (m, 1H, H4'), 3.85-3.65 (m, 3H, H5', CHCOOCH₃), 3.57 (s, 3H, CHCOOCH₃), 3.52 (d, *J* = 4.8, 2H, CH₂OH), 2.77-2.60 (m, 1H, H2'), 2.33-2.02 (m, 1H, H2').

¹³C (300 MHz, D₂O) δ 174.79 (d, *J* = 18), 155.28, 155.45, 148.42, 152.56, 139.64, 118.43, 85.89 (*J*(C,P) = 36.0), 83.61, 71.11 (d, *J*(C,P) = 18), 64.03 (d, *J*(C,P) = 21), 63.55 (d, *J*(C,P) = 24.0), 60.11, 57.38, 52.60, 38.87, 16.75.

35 ³¹P NMR (300 MHz, DMSO-*d*₆): δ 4.19

MS (ESI): [M-H] = 431.1 High res. MS (ESI): m/z calculated for $C_{14}H_{21}N_6O_8P$ 431.1080 [M-H], actual 431.1109.

5 2'-deoxy-adenosine-5'-serinyl-phosphoramidate (7) (MW = 418.29, $C_{13}H_{19}N_6O_8P$, yield 75.3%) was characterised as follows:

^1H NMR (300 MHz, D_2O): δ 8.36 (s, 1H), 8.13 (s, 1H), 6.39 (t, $J = 7.2$, 1H, H1'), 4.578 (dt, $J = 2.7, 5.4$, 1H, H3'), 4.20-4.13 (m, 1H, $CHCOOH$), 3.90-3.84 (m, 2H, H5'), 3.60-3.42 (m, 3H, H4', CH_2OH), 2.78-2.63 (m, 1H, H2'), 2.55-2.44 (m, 1H, H2').

10 ^{13}C (300 MHz, D_2O) δ 174.79 (d, $J(C,P) = 18$), 155.28, 155.45, 148.42, 152.56, 139.64, 118.43, 85.89 ($J(C,P) = 36.0$), 83.61, 71.11 (d, $J(C,P) = 18$), 64.03 (d, $J(C,P) = 21$), 63.55 (d, $J(C,P) = 24.0$), 60.11, 57.38, 52.60, 38.87, 16.75.

^{31}P NMR (300 MHz, D_2O): δ 7.28

MS (ESI): [M-H] = 417.1 High res. MS (ESI): m/z calculated for $C_{13}H_{19}N_6O_8P$ 417.0923 [M-H], actual 417.0912.

15

2'-deoxy-adenosine-5'-dimethylprolinyl-phosphoramidate (8a) (MW = 442.36, $C_{16}H_{23}N_6O_7P$, yield 38.9%) was characterised as follows:

20 ^1H NMR (300 MHz, $DMSO-d_6$): δ 8.43 (s, 1H), 8.13 (s, 1H), 7.28 (s, 2H NH_2), 6.35 (t, $J = 6.9$, 1H, H1'), 4.44 (s, 1H, H3'), 4.14-4.00 (s, 1H, H4'), 3.88-3.64 (m, 3H, H5', $CHCOOCH_3$), 3.53 (s, 3H, $CHCOOCH_3$), 3.25-3.10 (m, 2H, CH_2), 3.10-2.98 (m, 2H, CH_2), 2.97-2.83 (m, 2H, CH_2), 2.81-2.64 (m, 1H, H2'), 2.37-2.198 (m, 1H, H2'), 2.11-1.85 (m, 1H, H2').

MS (ESI): [M-1] = 441.1 High res. MS (ESI): m/z calculated for $C_{16}H_{23}N_6O_7P$ 441.1287 actual 441.1266.

25

2'-deoxy-adenosine-5'-prolinyl-phosphoramidate (8) (MW = 428.23, $C_{15}H_{21}N_6O_7P$, yield 64.5%) was characterised as follows:

30 ^1H NMR (300 MHz, $DMSO-d_6$): δ 8.32 (s, 1H), 8.13 (s, 1H), 6.37 (t, $J = 6.3$, 1H, H1'), 4.65-4.55 (m, 1H, H3'), 4.19-4.07 (m, 1H, H4'), 3.96-3.72 (m, 3H, H5', $CHCOOH$), 3.02-2.84 (m, 2H, CH_2), 2.83-2.60 (m, 1H, CH_2), 2.60-2.47 (m, 1H, CH_2), 2.04-1.83 (m, 1H, H2'), 1.76-1.47 (m, 3H, H2', CH_2).

MS (ESI): [M-1] = 427.1 High res. MS (ESI): m/z calculated for $C_{15}H_{21}N_6O_7P$ 427.1131 actual 427.1116.

35 EXAMPLE 2 – Biological assay

RT and DNA polymerase assays

Primers and templates used in the study (an underlined region is a sequence complementary to the primer):

- 5 SEQ ID NO:1 5'-³³P-CAGGAAACAGCTATGAC-3' (P1)
 SEQ ID NO:2 5'-CCCCTGTCATAGCTGTTTCCTG-3' (T1)
 SEQ ID NO:3 5'-CCTTTGTCATAGCTGTTTCCTCCCTTTGTCATAGCTGTTTCCTG-
 3' (T3)
 SEQ ID NO:4 5'-CTTTTTTTGTCATAGCTGTTTCCTGC-3' (T5)

10

³³P 5'-labeling of a primer (P1)

Labeling of a primer (200 pmol, P1) was accomplished with 5'-[γ-³³P]ATP (GE Healthcare) and T4 Polynucleotide kinase (NEB) and purified using Illustra™ MicroSpin™ G-25 columns (GE Healthcare).

15

Single nucleotide incorporation by HIV Reverse Transcriptases (HIV RT)

- A typical single nucleotide incorporation and primer extension assays using HIV RT polymerase was carried out similar to one described in the literature ADDIN. HIV RT polymerase was purchased from GE Healthcare and was supplied as either
 20 12 or 30 U/μL stock solution. The final concentration of HIV RT in a reaction mixture was 0.03-0.003 U/μL. A primer/template duplex mixture was prepared by combining appropriate amounts of a 5'-³³P-labeled primer (P1) and a template in 1:2 molar ratio to provide a 4X solution with 0.5 μM primer concentration. The polymerase reactions were carried out in a 5X RT buffer containing 250 mM TRIS·HCL, 250 mM KCl, 50
 25 mM MgCl₂, 2.5 mM spermidine, 50 mM DTT, pH 8.3. For the single nucleotide incorporation assay, a P1/T1 primer-template pair was used whereas the primer extension study was performed with P1/T3 and P1/T5 primer-template pairs.

- Briefly, a mixture containing 5 μL of the 4x primer/DNA duplex solution and 5 μL of 4x polymerase solution was pre-incubated at 37°C for 2 min to ensure
 30 formation a DNA polymerase/DNA duplex complex. Simultaneously, 2X solutions of dNTP to provide final concentrations of 100 μM, 200 μM, 500 μM, and 1 mM were also pre-incubated at 37°C for 2 min as well. The polymerase reaction in a total volume of 20 μL was initiated by addition of 10 μL of the 2X dNTP solution to the DNA polymerase/DNA duplex mixture. The reactions were run at 37°C and aliquots
 35 (2.5 μL) were removed at specified time points and mixed with 10 μL of a quenching buffer containing 80% formamide, 2 mM EDTA, 1X TBE. Quenched reactions were

analyzed by loading 2 μ L of a reaction sample onto a 20% denaturing polyacrylamide gel (19:1 acrylamide:bisacrylamide, 7M urea, 0.4mm $\times$ 30 cm $\times$ 40 cm) made in 1X TBE buffer (90mM Tris-borate, 2mM EDTA, pH 8.3). The gel was pre-equilibrated for 2 hours before loading and the reactions were run along with a tracking dye marker
5 containing bromophenol blue (BB) and xylene cyanol (XC) until the BB dye had run 2/3 of the total gel length. For visualization, gels were scanned using a Cyclone Phosphorimager.

Primer extension study with HIV RT and Terminator DNA polymerase was performed in a fashion similar to the single nucleotide incorporation experiments. Two
10 sets of primer/template complexes were used: P1/T3 and P1/T5.

Single nucleotide incorporation by Terminator DNA polymerase

In the case of Terminator DNA polymerase, the enzyme was obtained from Westburg (NEB) (2 U/ μ L) and the reactions were carried out in a 10X Thermopol
15 reaction buffer containing 20 mM TRIS·HCl, 10 mM KCl, 2 mM MgSO₄, 0.1% Triton X-100, pH 8.8. The final concentration of the Terminator DNA pol in the reaction mixture was 8.33×10^{-4} U/ μ L. The polymerase reaction involving Terminator DNA polymerase or any other thermostable polymerase (Vent (exo⁻), Taq DNA polymerase) was carried out in a similar way as the HIV RT reaction with some
20 modifications. The dNTP solutions and the primer/template/DNA polymerase mixture solutions were topped with mineral oil (30-60 μ L) and pre-incubated at 70°C for 2 min. The polymerase reactions were performed at 70°C as well.

Steady state kinetics of single nucleotide incorporation

25 The steady state kinetics of a single nucleotide incorporation of an amino acid phosphoramidate (AA-dAMP) and of a natural nucleoside triphosphate (dATP) was determined by the gel-based polymerase assay ADDIN. In all the experiments, the template T1 and the primer P1 were used (Table 1). The primer and template in 1:2 molar ratio were hybridized in a buffer containing 20 mM TRIS·HCl, 10 mM KCl, 2
30 mM MgSO₄, 0.1% Triton X-100, pH 8.8 and used in an amount to provide 125 nM concentration of the primer in each 12 μ L reaction. The range of concentrations for amino acid phosphoramidates was optimized according to a K_m value for the incorporation of an individual nucleotide. In the case of HIV RT (Amersham Bioscience (GE Healthcare), 30 U/ μ L), reaction mixtures containing the enzyme in
35 concentration to attain 5-20% conversion and appropriate substrate concentration (nucleoside phosphoramidate or natural dNTP) were incubated at 37°C and run for 8-

- 10 different time intervals. Kinetic analysis of single nucleotide incorporation by Terminator DNA polymerase (NEB, 2 U/ μ L) was performed similarly except the incubations and polymerase reactions, which were carried out at 70°C. To prevent solvent condensation/evaporation, the reaction mixtures were topped with mineral oil.
- 5 The reactions were quenched by addition of the buffer containing 80% formamide, 2 mM EDTA, 1X TBE buffer. The analysis of polymerase reactions was performed by polyacrylamide gel electrophoresis (20% (19:1 mono:bis), 7M urea, 30 cm $\times$ 40 cm $\times$ 0.4 mm). The relative band intensities were measured using OptiQuant software. The rates of incorporation (V) were calculated based on the percentage of the extension
- 10 production (n+1 band). The kinetic parameters ($V_{\max}$ and K_m) were determined by plotting V (pmol/min $\cdot$ U) versus substrate concentration and fitting the data point to a rectangular hyperbola using GraphPad Prism software.

EXAMPLE 3 - synthesis of oligonucleotides

15 Single nucleotide incorporation by HIV RT

- HIV reverse transcriptase is involved in the copying of the HIV genome and uses deoxy- and ribonucleotides as substrates. Furthermore, HIV RT is an error-prone polymerase and has high mutation rate. Therefore, the essential role of the HIV RT in viral replication and its flexibility and tolerance toward modified nucleotides
- 20 renders this enzyme a primary target in treatment of HIV infection. In the presented study, the ability of HIV RT to incorporate a series of amino acid phosphoramidate nucleoside analogs was investigated by the gel-based single nucleotide incorporation assay.

- Among amino acid phosphoramidate nucleosides (**1-6** and **1a-6a**), unexpected and remarkable results were observed with Asp-dAMP (**1**) (Figure 3).
- 25

- This phosphoramidate analog was recognized by HIV RT and efficiently incorporated into a growing primer strand resulting in 90% conversion to a (n+1) strand in 60 min (500 μ M nucleotide concentration). At the same conditions, incorporation of His-dAMP(**6**), Gly-dAMP (**3**), and Pro-dAMP (**8**) was 1.5, 6.5, and 3.7
- 30 fold less efficient, respectively. Efficient incorporation of Asp-dAMP (24.1%) was also observed when the substrate concentration was decreased 10 fold. However, significantly lesser incorporation of amino acid phosphoramidate was detected for nucleosides coupled to non-polar, hydrophobic amino acids. Ala-dAMP and Tyr-dAMP behaved as poor substrates leading to merely 7- and 10-fold reduction in
- 35 primer extension, respectively (Figure 4).

Interestingly, no incorporation occurred when respective methyl ester derivatives **1a-8a** were used as substrates in the polymerase reaction. Another unexpected result was observed with Glu-dAMP analog (**2**) that also acted very poorly as a HIV RT substrate. These observations suggest that recognition and incorporation of AA dAMPs are likely to be dictated by the chemical structure and electrostatics of the amino acid moiety.

Single nucleotide incorporation by Terminator DNA polymerase

Yet another polymerase enzyme that demonstrates similar trends in recognition and utilization of AA-dAMPs is Terminator DNA polymerase, a variant of (9°N-7) *Thermococcus* sp. DNA polymerase. This enzyme demonstrated effective recognition and incorporation of a number of nucleotides bearing unnatural nucleobase and sugar moieties ADDIN. Likewise, probing of AA-dAMP incorporation directed by Terminator DNA polymerase revealed property of analogs **1**, **3**, and **6** to act effectively as alternative substrates in the DNA polymerization reaction (Figure 5 and 6).

Yet again, the best results were obtained with Asp-dAMP, which led to 25.2% primer extension over 60 min at 500µM nucleoside concentration. At the same conditions, the similar results were obtained for Gly-dAMP and His-dAMP (26% and 25.4% primer extension, respectively). In the case of Glu-dAMP and methyl protected AA-dAMPs, Terminator DNA polymerase displays selectivity analogous to HIV reverse transcriptase and fails to direct incorporation of those phosphoramidate analogs (Figure 6).

Single nucleotide incorporation by other DNA polymerases

The remarkable property of Asp-dAMP encouraged further investigation and testing **1** as a substrate for other DNA polymerases. However, in the case of Taq, Vent (exo⁻), and KF (exo⁻) DNA polymerases, recognition and incorporation efficiency were significantly less appealing. Incorporation and primer extension were observed only in the case of KF (exo⁻) DNA pol demonstrating 32.5% conversion of the primer strand in 60 min. This is in contrast to Taq and Vent (exo⁻) DNA polymerases that failed to insert **1** into a growing primer strand. The diversity in incorporation selectivity that are observed among the polymerases (Terminator, Taq, Vent (exo⁻), KF (exo⁻), and HIV reverse transcriptase) could indicate the differences in the active site flexibility and tolerance to the triphosphate modifications (Figure 7).

Primer extension by HIV RT

The further investigation of Asp-dAMP recognition by the reverse transcriptase focused on ability of HIV RT to direct template dependent incorporation of more than one phosphoramidate nucleosides. For this purpose, template T3 containing a string of three thymidine nucleobases flanked with cytidine nucleobases at the 3' end and the template T5 that has an overhang of seven thymidine residues were used. Ability to HIV RT to synthesize a DNA sequence using phosphoramidate nucleotides as substrates was tested among Asp-dAMP, His-dAMP, Gly-dAMP, and Pro-dAMP.

Among this series of phosphoramidate nucleoside, the most encouraging results using T3 template were observed with Asp-dAMP and His-dAMP which were used by HIV RT to extend a primer with three adenine nucleobases (n+3 product) (Figure 8 and 9).

However, after 60 min of the polymerase reaction the (n+2) product predominates over the (n+3) product (56.3% vs. 5.2% for Asp-dAMP and 67.1% vs. 13.5% for His-dAMP). Interestingly, efficiency of DNA synthesis with His-dAMP at 500 μ M substrate concentration is similar or better to that when Asp-dAMP serves as the substrate (67.1% vs. 56.3%, respectively, for the synthesis of the (n+2) primer). This is in contrast to the single nucleotide incorporation results that indicate that His-dAMP is worse than Asp-dAMP as a substrate for HIV RT.

In the case of the T5 template with the overhang of seven thymidine nucleobases, HIV RT indeed generates (n+6) and (n+7) products at a very little extent while the (n+2) and (n+3) products are prevalent (Figure 10). The obvious stalling of the HIV RT polymerase after incorporation of two adenine nucleobases might indicate substrate inhibition or a template sequence effect. The primer strand extension for one hour with 500 μ M of Gly-dAMP or Pro-dAMP takes place with low efficiency and does not result in the formation of the full-length extension products.

Primer extension by Terminator DNA polymerase

The Terminator DNA pol mediated addition of amino acid phosphoramidate nucleosides instead of natural dNTPs at the 3' terminal end was investigated for several AA-dAMPs. Similarly, to the case of HIV RT, the best results were observed with AspdAMP phosphoramidate, which was successfully incorporated across from a string of thymidine residues (T3 template) to provide a (n+3) product (Figure 11).

However, when His-dAMP and Gly-dAMP were used as substrates for Terminator DNA polymerase, the primer extension took place with significantly lesser efficiency

(13.6% and 18.1% of primer extension, respectively) with the (n+1) product being predominant and halted after addition of two nucleoside phosphoramidate residues (Figure 12). The primer extension with Pro-dAMP was very ineffective and resulted only in addition of one nucleoside phosphoramidate residue at the primer's end.

5 In the case of the T5 template with the overhang of seven thymidine residues, the predominant product of the primer extension was the (n+2) oligonucleotide. Nonetheless, Terminator DNA polymerase was able to carry out the extension of the T5 primer with Asp-dAMP phosphoramidate and incorporate up to five adenine residues.

10

HIV Reverse Transcriptase

Steady state kinetics for single nucleotide incorporation was determined by the gel based polymerase assay. The kinetics analysis (Table 1) shows that $V_{\max}$ for incorporation of **1** is only 3 fold lower than that for a HIV RT natural substrate (dATP),
15 however, the K_m value for Asp-dAMP is 400 fold higher as compared to dATP. Therefore, as a result, the specificity, or a $V_{\max}/K_m$ value, for insertion of amino acid phosphoramidate against a natural nucleobase is reduced 1300 fold. The significantly higher K_m value for an unnatural amino acid phosphoramidate analog than one for the natural substrate suggests that the phosphoramidate substrate
20 dissociates from the active site more readily and faster. However, small difference in $V_{\max}$ values (3 fold) indicates that once the amino acid phosphoramidate substrate is bound at the active site nucleotidyl transfer takes place with the efficiency and the rate slightly lower than in the case of the natural substrate. It probably also indicates that the bound Asp-dAMP fits the polymerase active site well and adapts geometry
25 and orientation that closely resembles dATP.

TableSEQARABIC 2 - Steady state kinetics of Asp-dAMP incorporation by HIV RT

Substrate	$V_{\max}$ (pmol/min-U)	K_M (μ M)	$V_{\max}/K_M$ ($\times 10^6$)
dATP	8.39 $\pm$ 0.82	0.46 $\pm$ 0.15	18.1
1	2.63 $\pm$ 0.13	185.3 $\pm$ 24.55	0.014

30 EXAMPLE 4 - Primer extension experiments with novel aspartic acid phosphoramidate nucleotides

Highly purified 2'-deoxynucleoside triphosphates used in DNA polymerase reactions were purchased from Pharmacia.

Synthesis of aspartic acid phosphoramidate nucleosides

2'-Deoxynucleoside 5'-monophosphate (1.00 mmol) and L-aspartic acid methyl ester/N-Me-L-aspartic acid methyl ester (7.00 mmol) were dissolved in ^tBuOH (9.1 mL) and water (3.1 mL). A few drops of triethylamine were added to facilitate dissolution. Then, a solution of DCC (5.00 mmol) in ^tBuOH (6.7 mL) was added and the reaction mixture was refluxed for 2-3 hours while stirring under argon. The progress of the reaction was followed by TLC ⁱPrOH:NH₃:H₂O (7:1:2). Upon completion, the reaction mixture was cooled down and the solvents were removed by rotatory evaporation. The residue was resuspended in water and extracted with diethyl ether. The aqueous phase was then lyophilized. The residue was subjected to column chromatography on silica gel using the following solvent gradient: CHCl₃:MeOH (5:1), CHCl₃:MeOH:H₂O (5:2:0.25), CHCl₃:MeOH:H₂O (5:3:0.5), and finally CHCl₃:MeOH:H₂O (5:4:1). The product obtained was treated with 1.4 M K₂CO₃ (20 eq.) in MeOH-H₂O (1:2) and the reaction mixture was allowed to stir at room temperature. The course of the reaction was monitored by TLC ⁱPrOH:NH₃:H₂O (6:3:1) until the disappearance of the starting material. Then, the solvents were removed under reduced pressure. The residue was subjected to column chromatography on silica gel using the following solvent gradient: ⁱPrOH, ⁱPrOH:NH₃:H₂O (7:1:1).

2'-Deoxyadenosine-5'-N-methylaspartyl phosphoramidate (12)

The above general procedure was followed using 2'-deoxyadenosine 5'-monophosphate (80 mg, 0.24 mmol) and N-Me-L-aspartic acid methyl ester. After 2 h at reflux, the solid that was obtained was treated with 2.8 mL of 1.4M K₂CO₃ in MeOH-H₂O for 3 days. 2'-Deoxyadenosine-5'-methylaspartyl phosphoramidate (**12**, 58 mg, 52% for two steps) was obtained as a white solid which was characterised as follows.

¹H NMR (300 MHz, D₂O) δ 8.49 (1H, s), 8.24 (1H, s), 6.50 (1H, m), 4.72 (1H, m), 4.42-4.26 (2H, m), 3.99-3.97 (2H, m), 2.88-2.56 (2H, m), 2.52-2.35 (3H, m), 2.46 (3H, d, *J* = 9.2).

¹³C NMR (75 MHz, D₂O) δ 180.2, 179.8 (d, *J* = 5.1), 155.3, 152.5, 148.4, 139.7, 118.4, 86.0 (d, *J* = 9.1), 83.5, 71.1, 63.9 (d, *J* = 5.5), 59.5 (d, *J* = 3.7), 39.0, 38.6, 29.1 (d, *J* = 4.1).

³¹P NMR (121 MHz, D₂O): δ 9.03

HRMS calculated for C₁₅H₂₀N₆O₉P (M-H⁺) 459.10294, found 459.10365.

2'-Deoxyguanosine-5'-aspartyl phosphoramidate (9)

The above general procedure was followed using 2'-deoxyguanosine 5'-monophosphate (130 mg, 0.37 mmol) and L-aspartic acid methyl ester. After 2 h at reflux, the solid that was obtained was treated with 4.9 mL of 1.4M K₂CO₃ in MeOH-H₂O for 3 days. 2'-Deoxyguanosine-5'-aspartyl phosphoramidate (**9**, 104 mg, 60% for two steps) was obtained as a white solid which was characterised as follows.

¹H NMR (300 MHz, D₂O) δ 7.98 (1H, s), 6.16 (1H, m), 4.56 (1H, m), 4.10 (1H, m), 3.94-3.82 (2H, m), 3.67 (1H, m), 2.64 (1H, m), 2.52-2.35 (3H, m).

¹³C NMR (75 MHz, D₂O) δ 180.5 (d, *J* = 4.4), 178.5, 158.8, 153.8, 151.3, 137.4, 116.0, 85.9 (d, *J* = 9.9), 83.4 (d, *J* = 3.0), 71.4, 64.0 (d, *J* = 5.1), 54.2, 42.2 (d, *J* = 5.5), 38.6.

³¹P NMR (121 MHz, D₂O): δ 6.82

HRMS calculated for C₁₄H₂₀N₆O₁₀P (M+H⁺) 463.0979, found 463.09544.

2'-Deoxythymidine-5'-aspartyl phosphoramidate (10)

The above general procedure was followed using 2'-deoxythymidine 5'-monophosphate (125 mg, 0.39 mmol) and L-aspartic acid methyl ester. After 2 h at reflux, the solid that was obtained was treated with 5.3 mL of 1.4M K₂CO₃ in MeOH-H₂O for 3 days. 2'-Deoxythymidine-5'-aspartyl phosphoramidate (**10**, 127 mg, 75% for two steps) was obtained as a white solid which was characterised as follows..

¹H NMR (500 MHz, D₂O) δ 7.72 (1H, s), 6.27 (1H, m), 4.48 (1H, m), 4.07 (1H, m), 3.94-3.84 (2H, m), 3.71 (1H, m), 2.51-2.41 (2H, m), 2.30-2.24 (2H, m), 1.85 (3H, s).

¹³C NMR (125 MHz, D₂O) δ 180.5, 178.5, 166.2, 151.4, 137.1, 111.4, 85.5 (d, *J* = 9.1), 84.6, 70.9, 63.6, 54.2, 44.7, 38.2, 11.3.

³¹P NMR (202 MHz, D₂O): δ 6.54

HRMS calculated for C₁₄H₂₁N₃O₁₁P (M+H⁺) 438.09137, found 438.08937.

2'-Deoxycytidine-5'-aspartyl phosphoramidate (11)

The above general procedure was followed using 2'-deoxycytidine 5'-monophosphate (130 mg, 0.40 mmol) and L-aspartic acid methyl ester. After 2 h at reflux, the solid that was obtained was treated with 4.7 mL of 1.4M K₂CO₃ in MeOH-H₂O for 3 days. 2'-Deoxycytidine-5'-aspartyl phosphoramidate (**11**, 117 mg, 70% for two steps) was obtained as a white solid which was characterised as follows.

¹H NMR (300 MHz, D₂O) δ 7.96 (1H, d, *J* = 7.6), 6.32 (1H, t, *J* = 6.6), 6.13 (1H, d, *J* = 7.6), 4.53 (1H, m), 4.17 (1H, m), 4.00-3.98 (2H, m), 3.77 (1H, m), 2.62-2.48 (2H, m), 2.41 (1H, ddd, *J* = 3.7, *J* = 6.6, *J* = 14.0), 2.29 (1H, ddd, *J* = 6.6, *J* = 7.1, *J* = 14.0).

¹³C NMR (75 MHz, D₂O) δ 180.8 (d, *J* = 4.1), 179.0, 165.5, 156.8, 141.8, 96.4, 85.9, 85.7, 70.8, 63.8 (d, *J* = 5.0), 54.5, 42.8 (d, *J* = 6.2), 39.4.

^{31}P NMR (121 MHz, D_2O): δ 6.87

HRMS calculated for $\text{C}_{13}\text{H}_{18}\text{N}_4\text{O}_{10}\text{P}$ ($\text{M}-\text{H}^+$) 421.07606, found 421.07665.

Oligodeoxyribonucleotides

- 5 Primers and templates used to study the chain elongation reaction with different amino acid phosphoramidate derivatives.

SEQ ID NO:1 5'- ^{33}P -CAGGAAACAGCTATGAC-3' (P1)

SEQ ID NO:8 5'- ^{33}P -CAGGAAACAGCTATGACTGA-3' (P2)

SEQ ID NO:2 5'-CCCCTGTCATAGCTGTTTCCTG-3' (T1)

10 SEQ ID NO:5 5'-TTTTCGTCATAGCTGTTTCCTG-3' (T2)

SEQ ID NO:6 5'-AAAAAGTCAGTCATAGCTGTTTCCTG-3' (T4)

SEQ ID NO:7 5'-GTCATAGCTGTTTCCTG-3' (A)

- Oligodeoxyribonucleotides P1, P2, T1, T2, T4 and A were purchased from Sigma
15 Genosys. The concentrations were determined using a Varian Cary 300 Bio UV-spectrophotometer.

- The lyophilized oligonucleotides were dissolved in DEPC-treated water and stored at -20°C . The primer oligonucleotides were 5'- ^{33}P -labeled with 5'- $[\gamma\text{-}^{33}\text{P}]\text{ATP}$ (GE Healthcare) using T4 Polynucleotide kinase (NEB) following standard
20 procedures. Labeled oligonucleotides were further purified using IllustraTM MicrospinTM G-25 columns (GE Healthcare).

DNA polymerase reactions

- End-labeled primers were annealed to their template by combining primer and
25 templates in a molar ratio of 1:2 and heating the mixture to 70°C for 10 min, followed by slow cooling to room temperature over a period of 2.5 h. For the incorporation of L-Asp-dGMP (**9**), L-Asp-dTMP (**10**), L-Asp-dCMP (**11**), and *N*-Me-Asp-dAMP (**12**) (see Figure 13), the primer P1 was annealed to templates T1, T2, T4 or A and P2 was annealed to T4. A series of 20 μL reactions was performed for the enzyme HIV
30 reverse transcriptase (GE Healthcare, 30 U/ μL stock solution). The final mixture contained 125 nM primer-template complex, RT buffer (250 mM Tris-HCl, 250 mM KCl, 50 mM MgCl_2 , 2.5 mM spermidine, 50 mM DTT, pH 8.3), 0.03 U/ μL HIV RT and different amino acid phosphoramidates building blocks concentrations. In the control
35 reaction with the natural nucleotide, 10 μM or 50 μM dGTP, dTTP, dATP or dCTP were used. The mixture was incubated at 37°C for 3 min and aliquots were quenched after 5, 10, 20, 30, 60 and 120 min.

Kinetics experiments

To determine the kinetic parameters of the incorporation of Asp-dGMP (**9**), Asp-dTMP (**10**), Asp-dCMP (**11**) or dGTP, dTTP, dCTP, a steady-state kinetic assay was carried out. The reaction mixture was started by adding HIV reverse transcriptase to P1-T2, P1-T4 or P2T4 complex, buffer and Asp-dGMP, Asp-dTMP, Asp-dCMP or dGTP, dTTP, dCTP. The final mixture (20 μ L) contained 0.015 or 0.0075 U/ μ L HIV reverse transcriptase, buffer, 125 nM primer-template complex and various concentrations of Asp-dNMP or dNTP. A concentration range of 0.01-1 mM was used for Asp-dNPM and a concentration range of 0.1-10 μ M was used for dNTP. Reactions were incubated at 37 °C. Reaction times were between 1 and 120 min. The kinetic constants $V_{\max}$ and K_M were determined from a Michaelis–Menten plot, using GraphPad Prism version 3.02.

Electrophoresis

All polymerase reactions (3 μ L) were quenched by the addition of 10 μ L of loading buffer (90% formamide, 0.05% bromophenol blue, 0.05% xylene cyanol and 50 mM EDTA). Samples were heated at 70 °C for 5 min prior to analysis by electrophoresis for 2–3 h at 2000 V on a 0.4 mm 20% denaturing gel in the presence of a 100 mM Tris-borate, 2.5 mM EDTA buffer, pH 8.3. Products were visualized by phosphorimaging. The amount of radioactivity in the bands corresponding to the products of enzymatic reactions was determined by using the Optiquant image analysis software (Perkin Elmer).

In this example 4, we demonstrate that the L-aspartyl (**1**) and the L-histidyl (**6**) derivatives of dAMP can function as a substrate for human immunodeficiency virus reverse transcriptase type 1 (HIV-RT) and that chain elongation is possible. These experiments demonstrate that the polymerase enzyme is able to catalyse the cleavage of the relatively stable P-N bond and that an amino acid can be used as leaving group during the polymerization reaction.

In order to further characterize the potentiality of this leaving group, we studied the substrate properties L-Asp-dGMP(**9**), L-Asp-dTMP(**10**) and L-Asp-dCMP(**11**) for HIV-RT. Thus, the present work focuses on the ability of HIV RT to incorporate aspartic acid derivatives of 2'-deoxyguanosine-5'-monophosphate, 2'-deoxythymidine-5'-monophosphate, and 2'-deoxycytidine-5'-monophosphate into a growing DNA chain.

Kinetic analysis of L-Asp-dAMP (**1**) incorporation (in example 3) showed that the incorporation efficiency of this substrate by HIV RT was lower than that for the natural substrate (dATP). Therefore, we considered the possibility of activating the nucleoside monophosphate with modified aspartic acid derivatives. In this regard, we focused first attention on *N*-methyl-L-aspartic acid as leaving group. Thus, 2'-deoxyadenosine-5'-*N*-methylasspartyl phosphoramidate (**12**) was synthesized from 2'-deoxyadenosine-5'-monophosphate and *N*-methyl-L-aspartic acid methyl ester according to the method described by Wagner and coworkers.

The ability of HIV RT to incorporate 5'-*N*-methylasspartyl phosphoramidate **12** into a growing DNA chain was explored in a first series of gel-based single-nucleotide-incorporation assays with primer P1 and template T1 (Figure 14, panel I). Compound **12** is incorporated into the growing DNA strand but without base-pairing selectivity, since it is easily misincorporated opposite a cytosine base to form the corresponding n+2 product. The same infidelity in incorporation profile was found using lower polymerase concentration. The behavior of **12** is in contrast with that of the L-aspartic acid derivative **1**, which inserted selectively against thymine to give the n+1 product (as shown in example 3). When we carried out a control experiment with **12** and a mismatch sequence (A against A, P1T4, see Figure 15, panel I), phosphoramidate **12** misincorporated against adenine. Compound **12** is a good substrate for HIV-RT, but it shows reduced selectivity compared to other L-aspartic acid derivatives in these experiments. However, the incorporation of this compound **12** resembles most the properties of the natural substrate (dATP); thus compounds like 2'-deoxyadenosine-5'-*N*-methylasspartyl phosphoramidate (**12**) could be the best phosphate-modified nucleosides of the invention.

L-Asp-dGMP (**9**), L-Asp-dTMP (**10**), and L-Asp-dCMP (**11**) were synthesized according to a previously reported method. A series of gel-based single-nucleotide-incorporation assays was carried out (Figure 14), by using primer P1 and template T2 for guanine (**9**, Panel II), P1 and T4 for thymine (**10**, Panel III), and P2 and T4 for cytidine (**11**, Panel IV). As shown before for L-Asp-dAMP (**1**) in example 3, these three phosphoramidate analogues are recognized by HIV RT and are efficiently incorporated with base-pairing selectivity into the corresponding growing strand, resulting in 92% (**9**), 95% (**10**), and 82% (**11**) conversion to a n+1 strand in 60 min (500 μ M nucleotide concentration). It is interesting to note that no incorporation was observed when HIV RT was replaced for M-MLV reverse transcriptase, AMV reverse transcriptase and Φ -DNA polymerase.

To confirm that the former observations were due to a true base-pair extension instead to an extendase/terminal transferase activity we tried to extend a blunt ended duplex. With this purpose we carried out a third series of gel-based single-nucleotide-incorporation experiments with primer P1, template A (see Figure 15) and phosphoramidates **1**, **9**, **10** and **11**. As expected, none of these compounds incorporated at all into the growing DNA strand. Furthermore, control experiments with a mismatch sequence (G against A, P1T4, **9**; T against C, P1T2, **10**; C against T, P1T1, **11**; see Figure 15) confirmed a true base-pair extension, since primer elongation was not observed.

The efficiency of incorporation by HIV RT of compounds **9**, **10**, and **11** was investigated by determination of the kinetic parameters K_M and V_{max} . As observed before for **1** (as described in example 3), steady-state kinetic analysis (Table 3) of **9**, **10** and **11** incorporation indicated that, although K_M for the aspartic acid phosphoramidate analogues is significantly higher than for the natural substrates, the measured V_{max} is only 9-13 fold lower. These data suggest fast and efficient nucleophilic displacement of the amino acid moiety once the aspartic acid phosphoramidate is bound at the active site.

Table 3 - kinetics of incorporation of phosphoramidates **9**, **10** and **11** by HIV RT

Substrate	V_{max} (pmolmin ⁻¹ U)	K_M (μM)	V_{max}/K_M (×10 ⁶)
dGTP	28.81 ± 1.55	0.54 ± 1.55	53.4
9	2.143 ± 0.13	168.8 ± 27.93	0.013
dTTP	30.82 ± 1.44	0.53 ± 0.07	58.2
10	2.33 ± 0.22	288.2 ± 61.72	0.008
dCTP	5.62 ± 0.80	3.74 ± 0.95	1.5
11	0.59 ± 0.04	130.8 ± 19.8	0.005

Next, we analyzed the ability of HIV RT to direct template dependent selective incorporation of more than one different phosphoramidate nucleosides. For this purpose, primer P1 and template T2 containing an overhang of one cytidine and four thymine nucleobases at the 3' end were used. The ability of HIV RT to synthesize a DNA sequence with L-Asp-dGMP (**9**) and L-Asp-dAMP (**1**) was tested (Figure 16). We carried out first the incorporation of **9** into the growing primer DNA strand. After complete conversion to the n+1 product (two hours), compound **1** was added and the reaction was followed for two more hours. At this time, the n+2 product predominated over the n+1 product (80% vs 20%). In these experiments, stalling of the HIV RT

appeared after incorporation of two nucleotides. To confirm that the n+2 product formation is due to adenine incorporation instead of guanine misincorporation a control experiment was carried out. Primer P1, template T2 and compound **9** were used and the reaction was followed for four hours. As expected, no misincorporation was observed, the n+1 conversion at 4 hours is the same as observed at 2 hours (95% incorporation).

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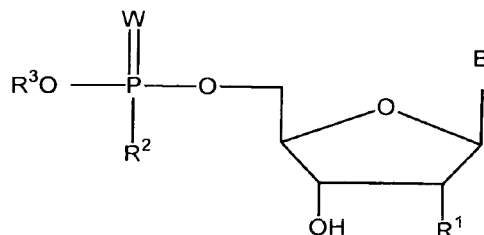
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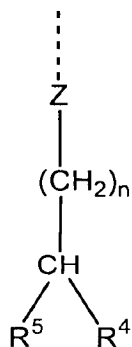
CLAIMS

1. A phosphate-modified nucleoside represented by the structural formula III:



5 wherein

- B is a pyrimidine or purine base, or an analogue thereof, optionally substituted with one or two substituents independently selected from the group consisting of halogen, hydroxyl, sulfhydryl, methyl, ethyl, amino and methylamino;
- 10 - R¹ is H or OH;
- R³ is selected from the group consisting of H, C₁-₆ alkyl, C₃-₆ cycloalkyl, aryl-C₁-₆alkyl and 2-cyanoethyl, wherein said C₁-₆ alkyl, C₃-₆ cycloalkyl or aryl-C₁-₆ alkyl is optionally substituted with one or more, preferably 1, 2 or 3, substituents independently selected from the group consisting of halogen, OH, C₁-₆ alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano and amino;
- 15 - W is O or S; and
- R² is a group represented by the structural formula IV:



20 wherein

- n is 0 or 1;

- Z is selected from the group consisting of O, S, NH and NCH₃;
 - each of R⁴ and R⁵ is independently selected from the group consisting of hydrogen, (CH₂)_m-COOR⁶; and (CH₂)_m-imidazolyl, provided that R⁴ and R⁵ are not both hydrogen;;
 - R⁶ is H or C₁₋₆ alkyl;
 - m is 0, 1 or 2; and
 - dotted lines represent the point of attachment of Z to the phosphorous atom of formula (III);
- 10 stereoisomers, pharmaceutically acceptable salts and pro-drugs thereof, provided that said phosphate-modified nucleoside is not:
- N-5'-adenylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,
 - N-5'-uridylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,
 - N-5'-thimidylylphosphoramidate L-aspartic acid 1,4-dimethyl ester,
 - N-5'-adenylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,
 - N-5'-guanylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,
 - N-5'-uridylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,
 - N-5'-thymidylylphosphoramidate L-aspartic acid 1,4-dimethyl ester, monoammonium salt,
 - N-5'-citidylylphosphoramidate L-aspartic acid disodium salt,
 - N-5'-uridylylphosphoramidate L-histidine
 - N-5'-uridylylphosphoramidate L-histidine 1-methyl ester,
 - N-5'-adenylylphosphoramidate L-histidine 1-methyl ester,
 - N-5'-cytidylylphosphoramidate L-histidine 1-methyl ester, or
 - N-5'-uridylylphosphoramidate L-aspartic acid.

2. The phosphate-modified nucleoside of claim 1 wherein n is 0.

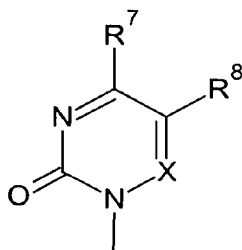
3. The phosphate-modified nucleoside of claim 1 or 2 wherein Z is NH.
4. The phosphate-modified nucleoside of any of claims 1 to 3 wherein R⁴ is
5 COOH and R⁵ is selected from the group consisting of CH₂-COOH, CH₂-(3H-imidazol-4-yl) and (CH₂)₂-COOH.
5. The phosphate-modified nucleoside of any of claims 1 to 4 wherein R³ is H;
Z is NH; R⁴ is COOH; and R⁵ is selected from the group consisting of CH₂-
10 COOH, CH₂-(3H-imidazol-4-yl) and (CH₂)₂-COOH.
6. The phosphate-modified nucleoside of any of claims 1 to 5, being selected
from the group consisting of 2'-deoxy-adenosine-5'-aspartyl-phosphoramidate
(Asp-dAMP); 2'-deoxy-cytidine-5'-aspartyl-phosphoramidate (Asp-dCMP); 2'-
15 deoxy-guanosine-5'-aspartyl-phosphoramidate (Asp-dGMP); 2'-deoxy-
thymidine-5'-aspartyl-phosphoramidate (Asp-dTMP); and 2'-deoxy-uridine-5'-
aspartyl-phosphoramidate (Asp-dUMP).
7. The phosphate-modified nucleoside of any of claims 1 to 5, being selected
20 from the group consisting of adenosine-5'-aspartyl-phosphoramidate (Asp-
AMP); cytidine-5'-aspartyl-phosphoramidate (Asp-CMP); guanosine-5'-
aspartyl-phosphoramidate (Asp-GMP); 5-methyluridine-5'-aspartyl-
phosphoramidate (Asp-m5uMP); and uridine-5'-aspartyl-phosphoramidate
(Asp-UMP).
- 25
8. The phosphate-modified nucleoside of any of claims 1 to 5, being selected
from the group consisting of of 2'-deoxy-adenosine-5'-histidyl-
phosphoramidate (His-dAMP); 2'-deoxy-cytidine-5'-histidyl-phosphoramidate
(His-dCMP); 2'-deoxy-guanosine-5'-histidyl-phosphoramidate (His-dGMP); 2'-
30 deoxy-thymidine-5'-histidyl-phosphoramidate (His-dTMP); and 2'-deoxy-
uridine-5'-histidyl-phosphoramidate (His-dUMP).

9. The phosphate-modified nucleotide of any of claims 1 to 5, being selected from the group consisting of adenosine-5'-histidyl-phosphoramidate (His-AMP); cytidine-5'-histidyl-phosphoramidate (His-CMP); guanosine-5'-histidyl-phosphoramidate (His-GMP); 5-methyluridine-5'-histidyl-phosphoramidate (His-m5uMP); and uridine-5'-histidyl-phosphoramidate (His-UMP).

10. The phosphate-modified nucleoside of any of claims 1 to 4 wherein R^3 is H; Z is NH; R^4 is COOCH_3 ; and R^5 is selected from the group consisting of $\text{CH}_2\text{-COOCH}_3$, $\text{CH}_2\text{-(3H-imidazol-4-yl)}$ and $(\text{CH}_2)_2\text{-COOCH}_3$.

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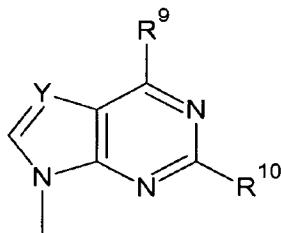
11. The phosphate-modified nucleoside of any of claims 1 to 4 wherein said pyrimidine analogue is represented by the structural formula (B):



wherein

- 15
- R^7 is selected from the group consisting of $-\text{OH}$, $-\text{SH}$, $-\text{NH}_2$, $-\text{NHCH}_3$ and $-\text{NHC}_2\text{H}_5$;
 - R^8 is selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, amino, ethylamino, trifluoromethyl, cyano and halogen; and
- 20
- X is CH or N.

12. The phosphate-modified nucleoside of any of claims 1 to 4 wherein said purine analogue is represented by the structural formula (D):



wherein

- R⁹ is selected from the group consisting of H, -OH, -SH, -NH₂, and -NHCH₃;
- R¹⁰ is selected from the group consisting of hydrogen, methyl, ethyl, hydroxyl, amino and halogen; and
- Y is CH or N.

13. The use of the phosphate-modified nucleosides of any of claims 1 to 12 as a substrate for a DNA/RNA polymerase.
14. The use of claim 13 in bacteriae or *in vitro*.
15. The use of claim 13 or claim 14, wherein said polymerase is from a micro-organism or from bacterial or viral origin.
16. The use of any of claims 13 to 15, wherein the polymerase is Terminator DNA polymerase; KF (exo⁻) DNA polymerase or Reverse Transcriptase (e.g. HIV-RT).
17. The use of any of claims 13 to 16 to build in at least one nucleotide in a growing DNA- or RNA-strand.
18. The use of claim 17 to build in at least 2 nucleotides in a growing DNA- or RNA-strand.
19. The use of claim 17 or claim 18 to build in at most 300 nucleotides in a growing DNA- or RNA-strand.
20. The use of the phosphate-modified nucleosides of any of claims 1 to 12 for incorporation into oligonucleotides.

21. A non-pharmaceutical composition comprising a phosphate-modified nucleoside according to any of claims 1 to 12, an aqueous solution and optionally one or more buffering agents.
- 5 22. The composition of claim 21, further comprising one or more nucleoside triphosphates (NTP).
23. The composition of claim 22, wherein said one or more nucleoside triphosphates consists of a mixture of natural NTPs selected from the group
- 10 consisting of ATP, CTP, GTP, UTP and TTP.
24. The use of a composition according to any of claims 21 to 23 as a substrate to build in at least one nucleotide in a growing DNA- or RNA-strand.
- 15 25. A pharmaceutical composition comprising a therapeutically effective amount of a phosphate-modified nucleoside according to any of claims 1 to 12, and one or more pharmaceutically acceptable excipients.
26. The use of the phosphate-modified nucleosides of any of claims 1 to 12 as
- 20 a substrate for the growth of bacteriae.
27. The phosphate-modified nucleosides of any of claims 1 to 12 for use as a medicine.
- 25 28. The use of the phosphate-modified nucleosides of any of claims 1 to 12 for the manufacture of a medicament for the prevention or treatment of a viral infection in a mammal.
29. The use of claim 28, wherein said viral infection is a HIV infection.
- 30 30. The use of claim 28 or claim 29, wherein said mammal is a human being.

31. A method of prevention or treatment of a viral infection in a mammal, comprising the administration of a therapeutically effective amount of a phosphate-modified nucleoside according to any of claims 1 to 12, optionally in combination with one or more pharmaceutically acceptable excipients.

5

32. The method of claim 31, wherein said viral infection is a HIV infection.

33. The method of claim 31 or claim 32, wherein said mammal is a human being.

10

34. The use of the phosphate-modified nucleosides of any of claims 1 to 12 as a substrate for wild type or mutated polymerases for *in vitro* production of DNA, RNA, peptides or proteins.

15 35. The use of the phosphate-modified nucleotides of any of claims 1 to 12 for performing PCR.

36. The phosphate-modified nucleoside of any of claims 1 to 5, being 2'-deoxy-adenosine-5'-aspartyl-phosphoramidate, 2'-deoxy-adenosine-5'-glutamyl-phosphoramidate or 2'-deoxy-adenosine-5'-histidylphosphoramidate.

37. The phosphate-modified nucleoside of any of claims 1 to 3, being selected from the group consisting of 2'-deoxy-adenosine-5'-dimethylaspartyl-phosphoramidate; 2'-deoxy-adenosine-5'-dimethylglutamyl-phosphoramidate; and 2'-deoxy-adenosine-5'-methylhistidyl phosphoramidate.

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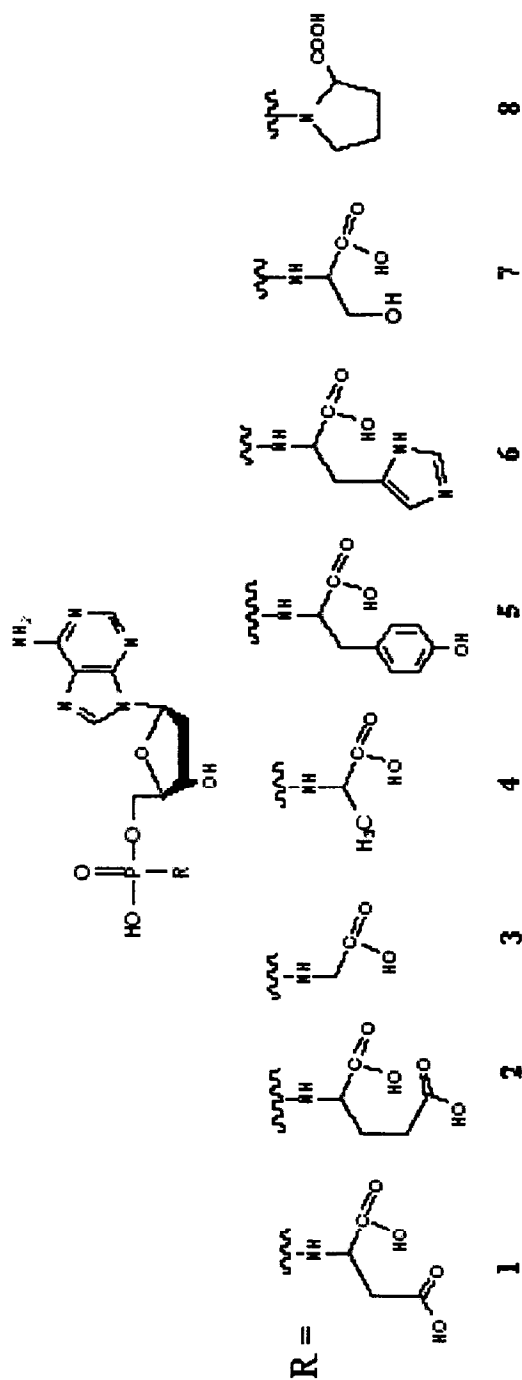


Figure 1

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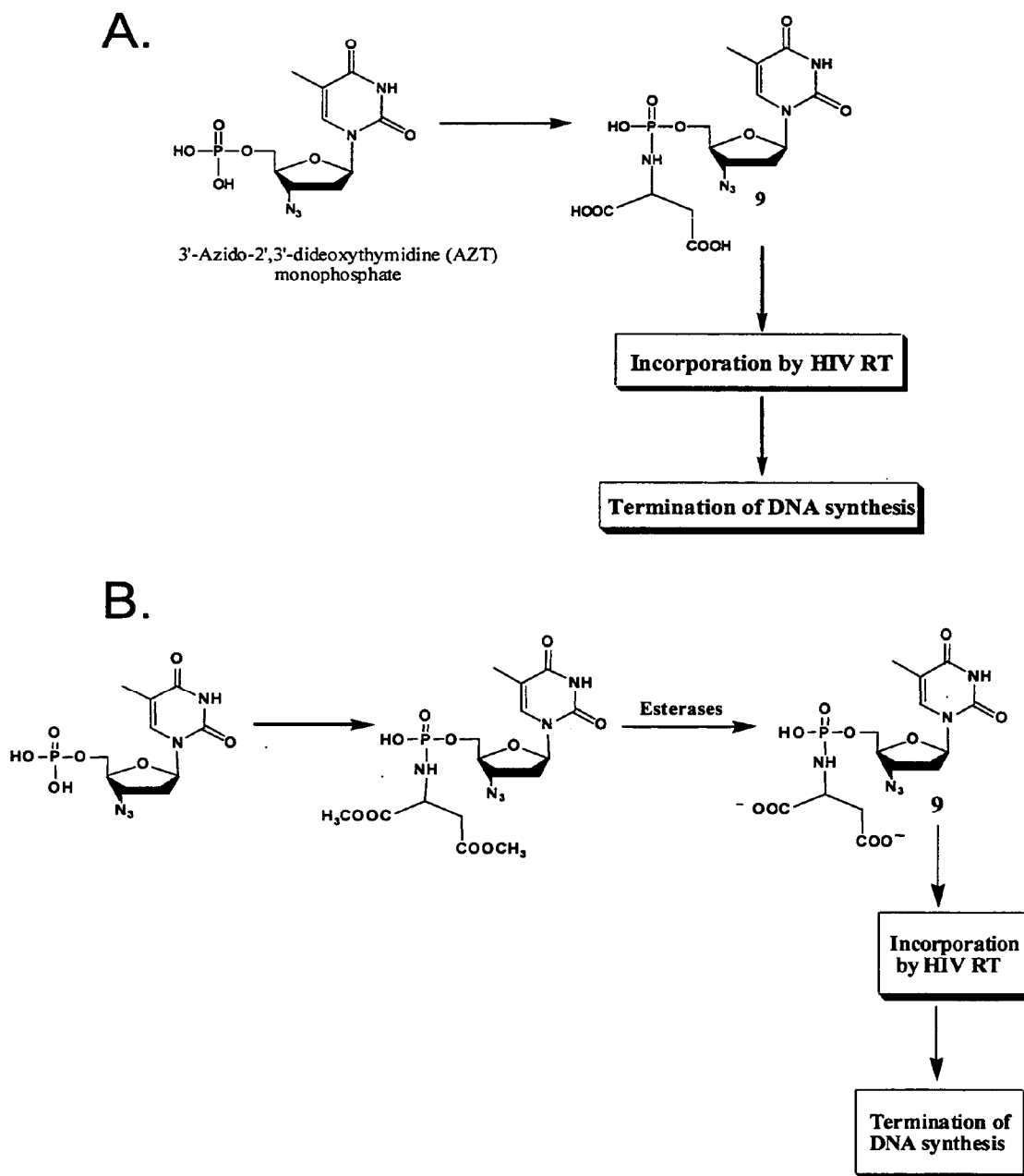


Figure 2

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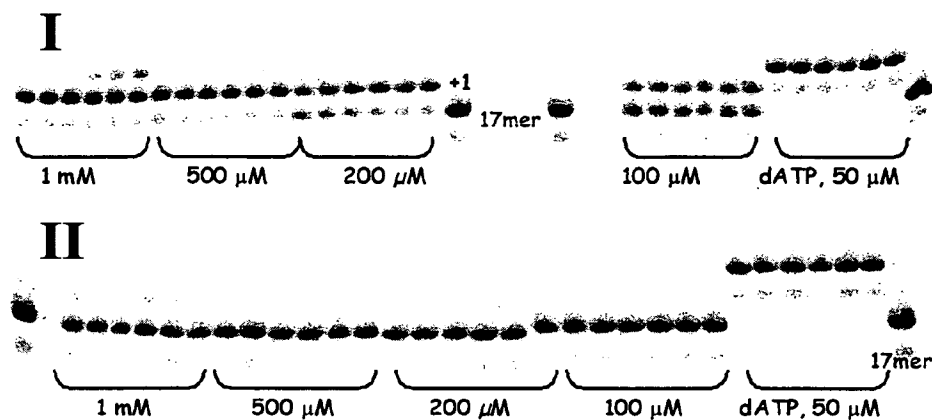


Figure 3

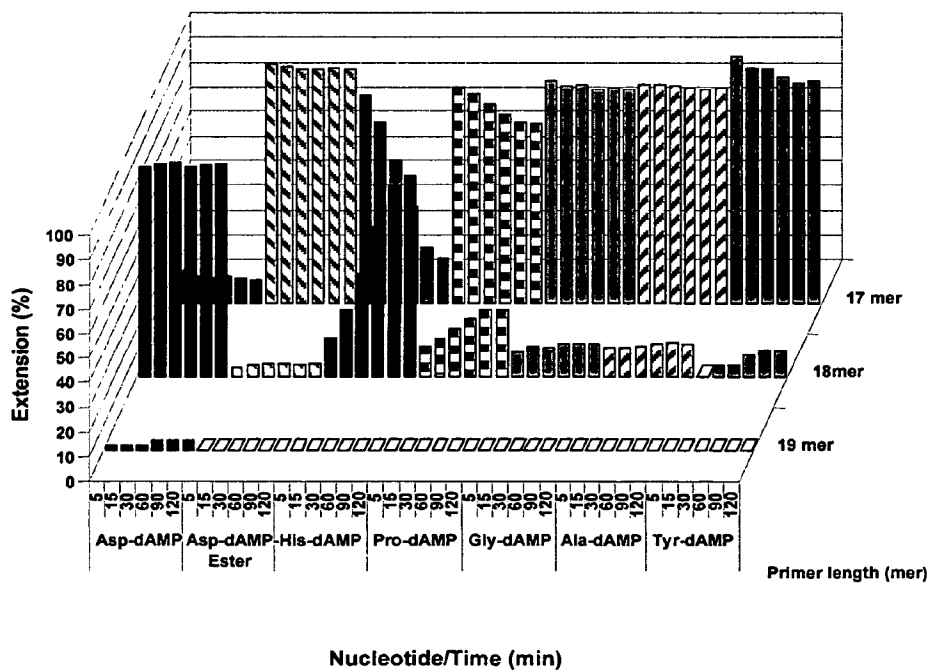
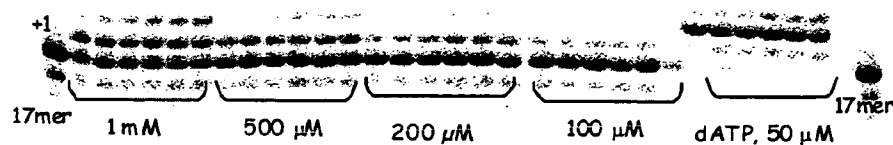


Figure 4

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I



II

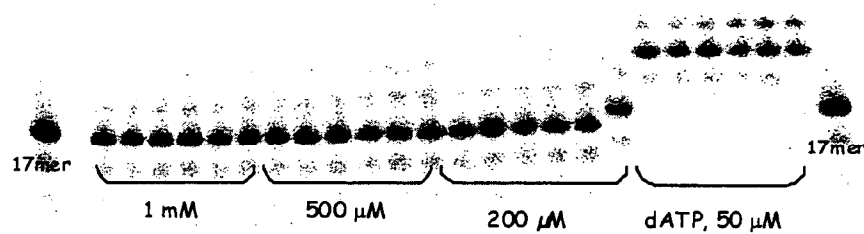


Figure 5

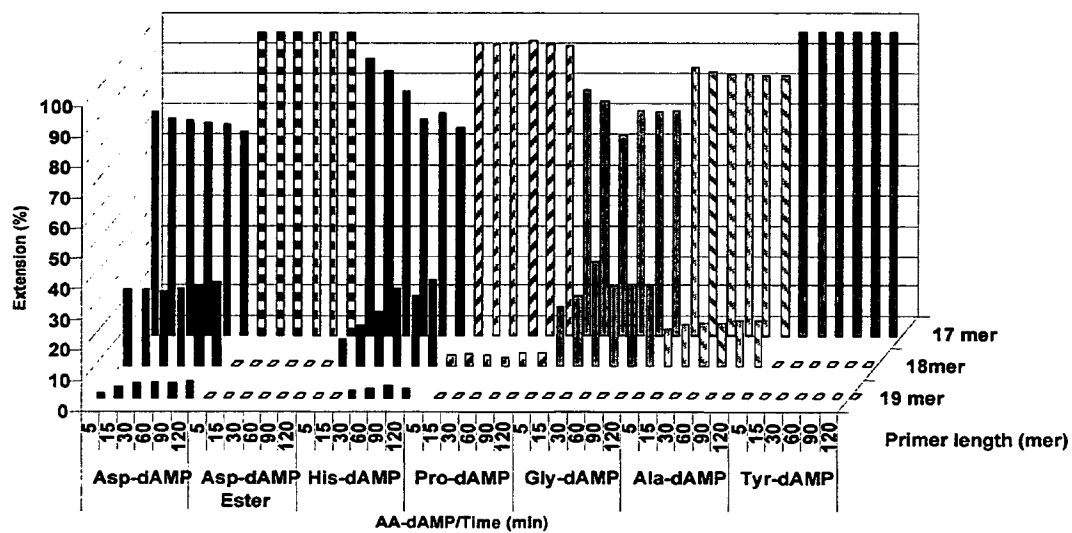
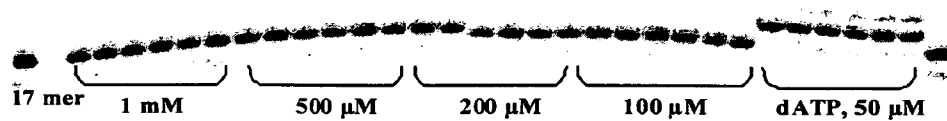


Figure 6

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I.



II.



III.

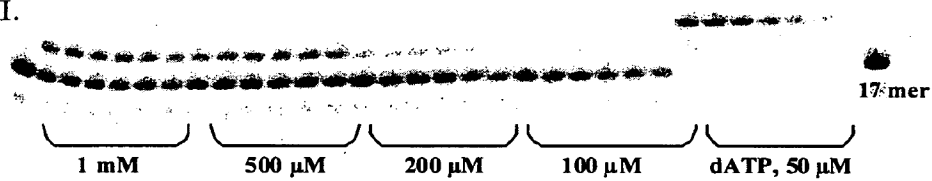


Figure 7

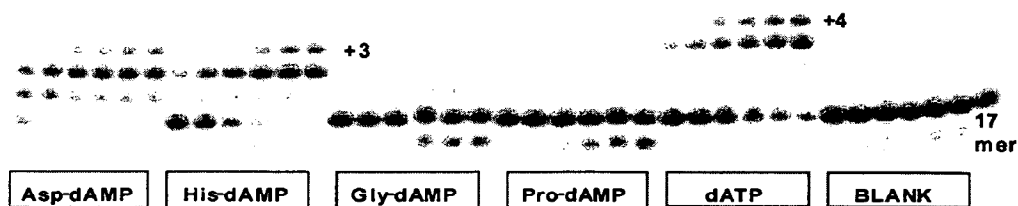


Figure 8

6/11

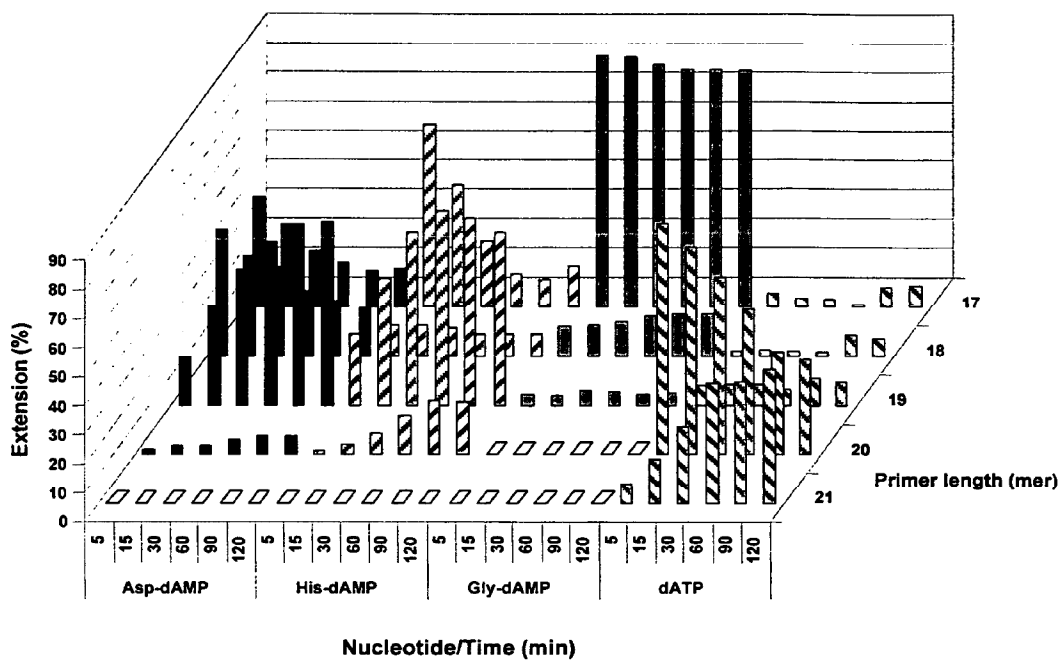


Figure 9

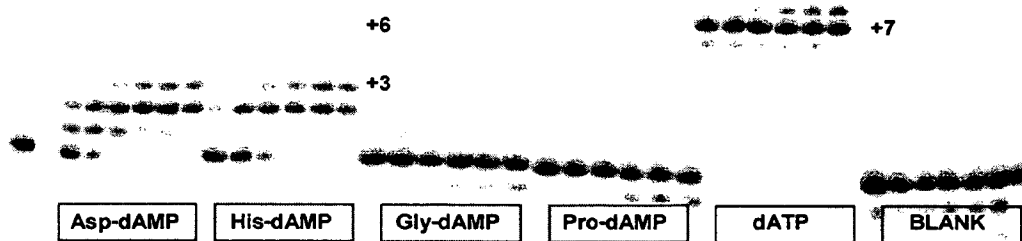


Figure 10

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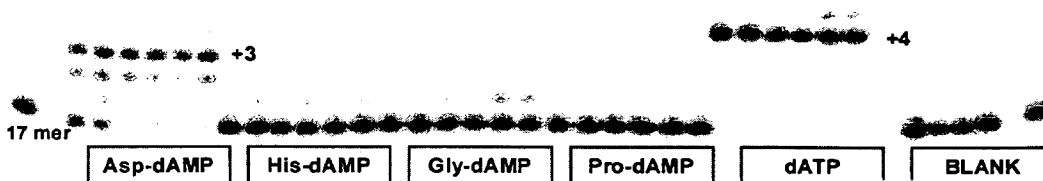


Figure 11

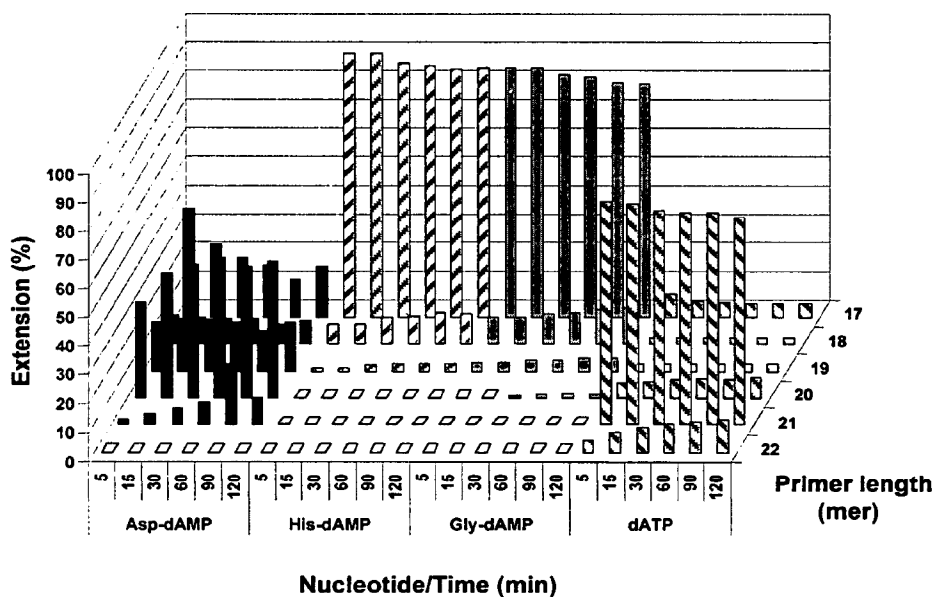


Figure 12

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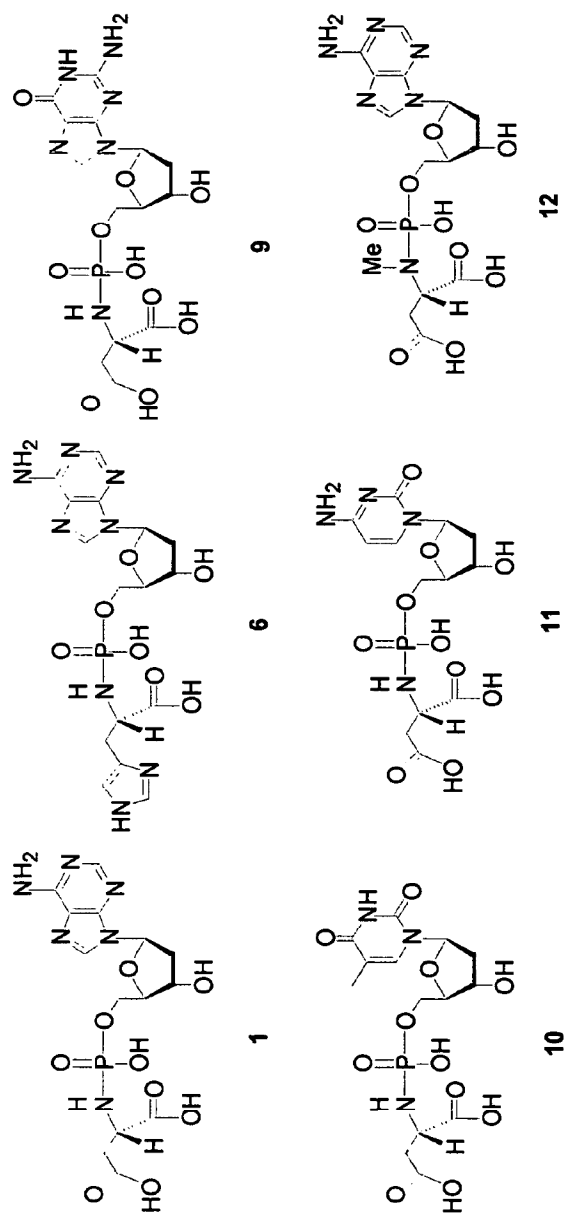


Figure 13

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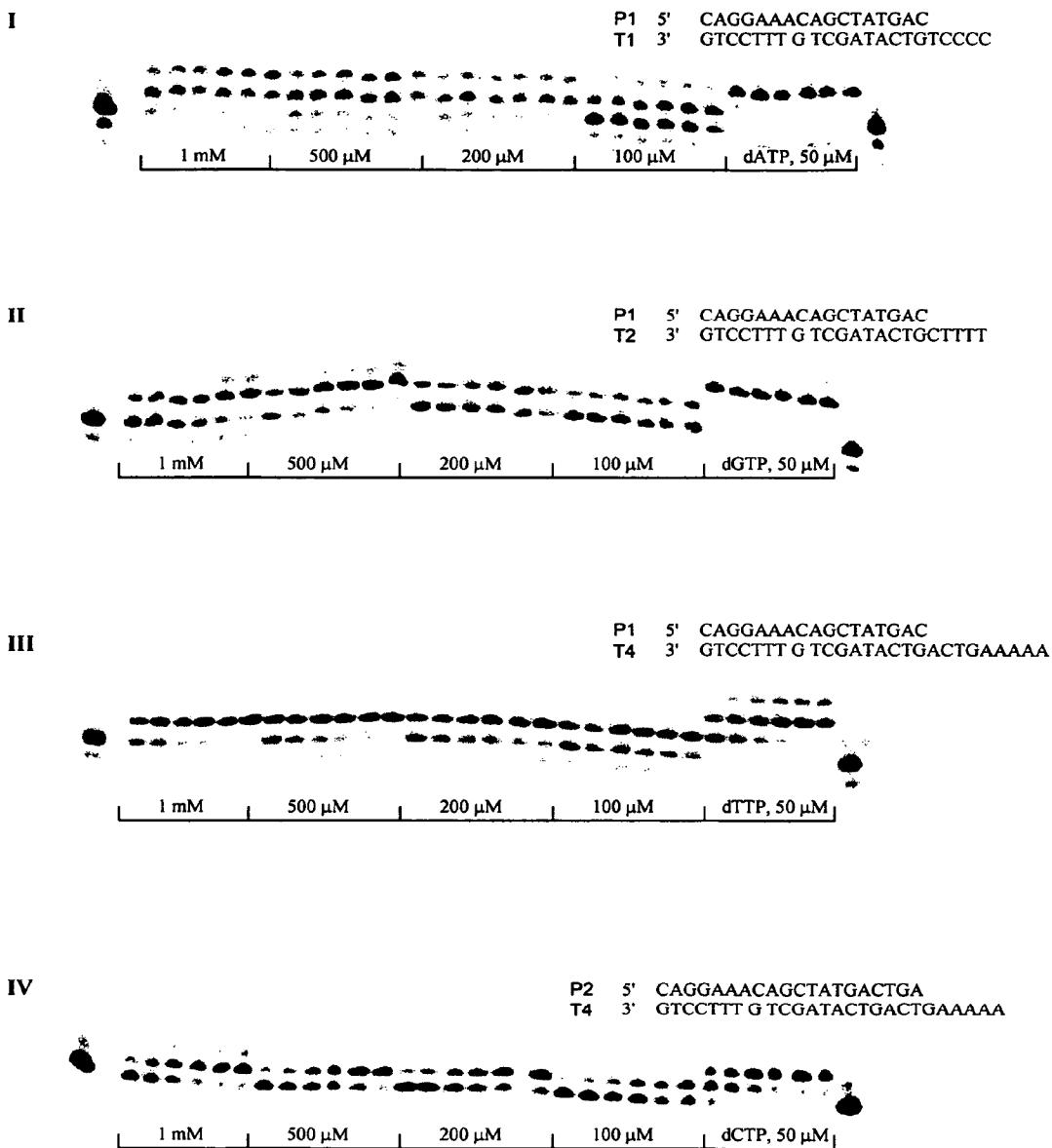


Figure 14

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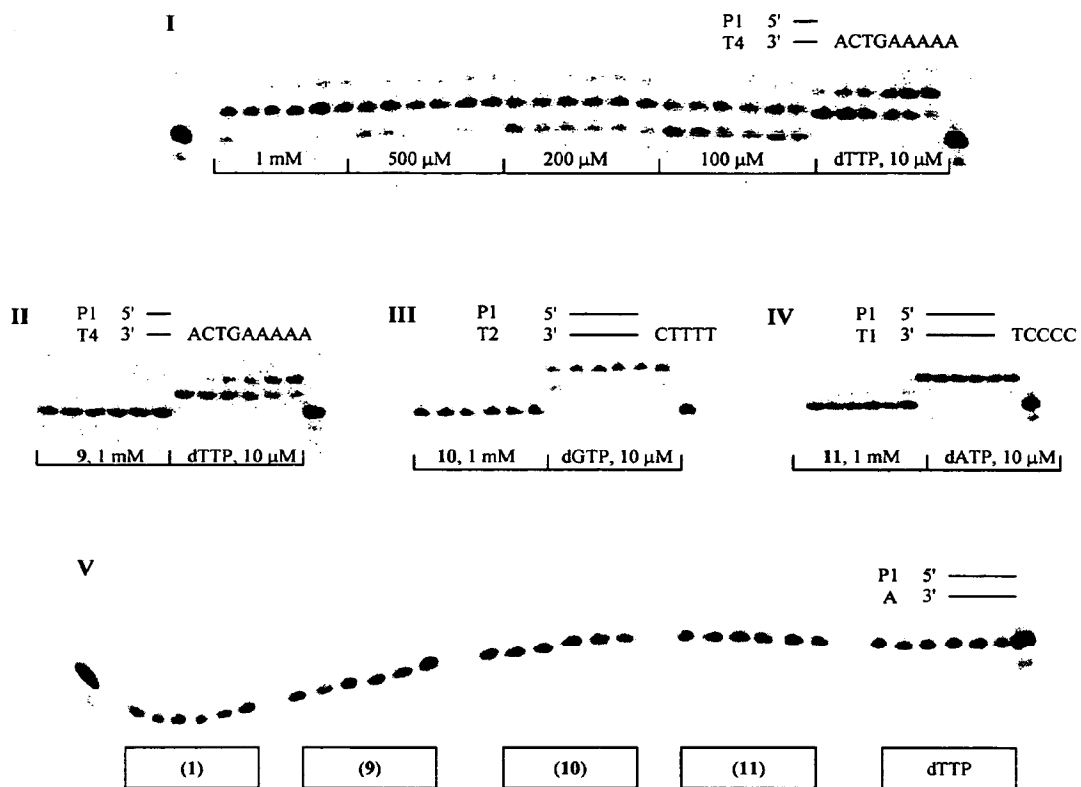


Figure 15

11/11

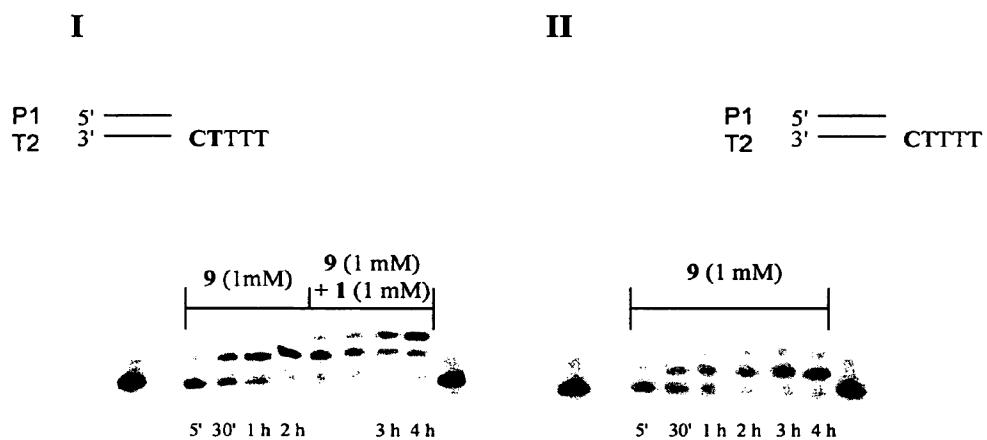


Figure 16

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gilead Sciences, Inc.

Application No.: 17/077,267

Confirmation No.: 4237

Filed: October 22, 2020

Art Unit: 1623

For: NUCLEOSIDE PHOSPHORAMIDATE
PRODRUGS

Examiner: Patrick T. Lewis

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This Amendment is responsive to the Final Office Action dated September 22, 2022, concerning the above-referenced patent application. The Office set forth a three-month period to reply. Accordingly, this reply is timely filed before its due date of December 22, 2022. In response to the Action, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing amendments and in view of the reasons that follow.

Amendments to the Claims

By this paper, claims 14-16 and 19 are canceled without prejudice or disclaimer. Claim 13 is amended to incorporate the limitations previously recited in claim 16; claim 17 is amended to update dependency; and claim 18 is amended to be an independent claim.

The amendments of the claims are made in an effort to place the application in condition for allowance and do not introduce any subject matter not yet considered by the Office. Therefore, entry of the claim amendment is respectfully requested after the Final Office Action. Upon such entry, claims 13 and 17-18 are currently pending and under examination.

Rejection under 35 U.S.C. § 103

Claims 13-15 and 19 are rejected under pre-AIA 35 U.S.C. 103(a) as allegedly being unpatentable over WO 2005/003147 A2 (hereinafter “Clark”) and Perrone et al., J. Med. Chem. (2007), Vol. 50, pages 1840-1849 (hereinafter “Perrone”) in combination.

Without acquiescing to the propriety of the rejection, but in a sincere attempt to expedite prosecution, claims 14, 15, and 19 have been canceled, and claim 13 has been amended to incorporate the limitations of previous claim 16. Accordingly, claim 13 is now patentable for at least the same reasons that support the patentability of previous claim 16. Thus, Applicant respectfully requests that the rejection be withdrawn.

Claim Objections/Allowable Subject Matter

Applicant thanks the Office for acknowledging that claims 16-18 would be allowable if rewritten in independent form. As discussed above, claim 16 has been canceled, and claims 17-18 have been amended, rendering the claim objections moot.

CONCLUSION

Applicant believes that the present application is now in condition for allowance.
Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-4561. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 50-4561.

Respectfully submitted,

Dated: November 15, 2022

By Joy Lynn Nemirow/
Joy Lynn Nemirow, Ph.D.
Registration No.: 67,163
Attorney for Applicant
SHEPPARD MULLIN RICHTER & HAMPTON LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626
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Customer Number: 117796

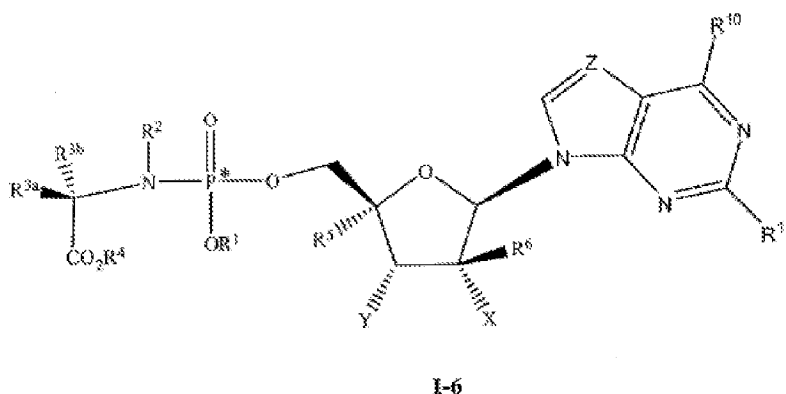
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1.-12. (Canceled)

13. (Currently Amended) A compound of formula **I-6**:



wherein:

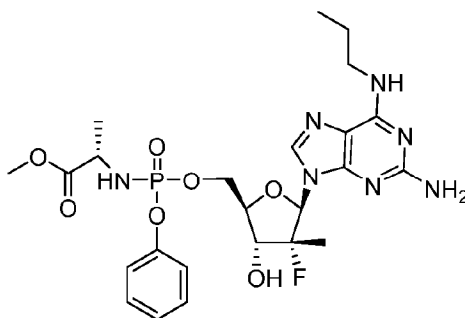
- (a) R^1 is H, -CH₃, phenyl, p-bromo-phenyl, p-chloro-phenyl or p-fluoro-phenyl;
- (b) R^2 is H;
- (c) R^{3a} is H and R^{3b} is H, -CH₃, -CH(CH₃)₂, -CH₂CH(CH₃)₂, -CH(CH₃)CH₂CH₃, -CH₂Ph or lower cycloalkyl;
- (d) R^4 is ~~hydrogen~~, -CH₃, ethyl, *n*-propyl, *i*-propyl, ~~*n*~~-butyl, 2-butyl, ~~*i*~~-butyl, ~~benzyl~~, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, N-methyl-aziridin-2-yl, N-methyl-azetidin-3-yl, N-methyl-pyrrolidin-3-yl, N-methyl-pyrrolidin-4-yl, N-methyl-piperidin-4-yl, lower haloalkyl or di(C₁₋₆ alkyl)amino-C₁₋₆ alkyl;
- (e) R^5 is H;
- (f) R^6 is H, -CH₃, -CH₂F, -CHF₂, -CF₃ or -F;
- (g) X is H, -OH, -OCH₃, -F, -NH₂ or -N₃;

with the proviso that X cannot be OH when R^6 is -CH₃ or -CH₂F;

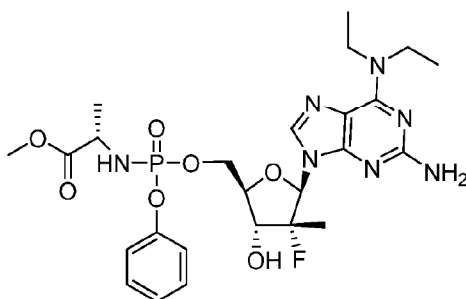
- (h) Y is -OH, -NH₂, -OCH₃ or -OC(O)CH₃;
- (i) ~~R¹⁰ is -NHR' and R¹¹ is -NH₂; R¹⁰ and R¹¹ are independently H, F, Br, I, OH, OR', NH₂, NHR', NR'₂, CO₂R', CONH₂, CONHR', CONR'₂, CH=CHCO₂H or CH=CHCO₂R',~~
 with the proviso that when R¹⁰ is -OH, R¹¹ is not -NH₂;
- (j) Z is N or -CR¹²;
 wherein R¹² is H, halogen, -OR', -NH₂, -NHR', -NR'₂, -NO₂, C₁₋₆ alkyl, -CO₂R', -CONH₂, -CONHR', -CONR'₂, -CH=CHCO₂H or -CH=CHCO₂R';
- (k) R' is C₁₋₆ alkyl, ~~a lower cycloalkyl or C(O)(C₁₋₆ alkyl) or alternatively, in the instance of -NR'₂, each R' comprise at least one C atom that are joined to form a heterocycle comprising at least two carbon atoms;~~ and
- (l) P* is a chiral phosphorus atom;
 or a pharmaceutically acceptable salt thereof.

14.-16. (Canceled)

17. (Currently Amended) The compound of claim ~~[[16]]~~13, or a pharmaceutically acceptable salt thereof, wherein the compound has a formula:



18. (Currently Amended) ~~The compound of claim 15, or a pharmaceutically acceptable salt thereof, wherein the~~A compound has a formulawhich is:



or a pharmaceutically acceptable salt thereof.

19. (Canceled)

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 17/077,267		Filing Date 10/22/2020		☐ To be Mailed			
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO											
APPLICATION AS FILED - PART I											
		(Column 1)		(Column 2)							
FOR		NUMBER FILED		NUMBER EXTRA		RATE (\$)		FEE (\$)			
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A		N/A		N/A					
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))		N/A		N/A		N/A					
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A		N/A		N/A					
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *				x \$100 =					
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *				x \$480 =					
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).									
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))											
* If the difference in column 1 is less than zero, enter "0" in column 2.						TOTAL					
APPLICATION AS AMENDED - PART II											
AMENDMENT	11/15/2022	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR		(Column 3) PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	* 3		Minus ** 20		= 0		x \$100 =		0	
	Independent (37 CFR 1.16(h))	* 2		Minus *** 3		= 0		x \$480 =		0	
	☐ Application Size Fee (37 CFR 1.16(s))										
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
								TOTAL ADD'L FEE		0	
AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR		(Column 3) PRESENT EXTRA		RATE (\$)		ADDITIONAL FEE (\$)	
	Total (37 CFR 1.16(i))	*		Minus **		=		x \$0 =			
	Independent (37 CFR 1.16(h))	*		Minus ***		=		x \$0 =			
	☐ Application Size Fee (37 CFR 1.16(s))										
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))										
								TOTAL ADD'L FEE			
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.								LIE			
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".								/YOLANDA CHADWICK/			
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".											
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.											

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Issue Classification 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

CPC						
Symbol					Type	Version
A61K	/	31	/	7072	F	2013-01-01
A61K	/	31	/	706	I	2013-01-01
A61K	/	31	/	7064	I	2013-01-01
A61K	/	31	/	7076	I	2013-01-01
C07H	/	19	/	04	I	2013-01-01
C07H	/	19	/	20	I	2013-01-01
C07H	/	19	/	06	I	2013-01-01
C07H	/	19	/	10	I	2013-01-01
A61K	/	45	/	06	I	2013-01-01
C07H	/	17	/	02	I	2013-01-01
C07D	/	417	/	14	I	2013-01-01
Y02A	/	50	/	30	A	2018-01-01
A61K	/	31	/	7068	A	2013-01-01
C07H	/	19	/	073	A	2013-01-01

CPC Combination Sets					
Symbol	Type	Set	Ranking	Version	
/		/			

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	3	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	01 December 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20221201

Issue Classification 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	31	/ 7076
NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
514	23

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	3	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	01 December 2022	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20221201

Issue Classification 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		10		19										
	2		11												
	3		12												
	4		13												
	5		14												
	6		15												
	7		16												
	8		17												
	9		18												

NONE (Assistant Examiner) _____ (Date) _____		Total Claims Allowed: 3	
/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623 (Primary Examiner) _____ (Date) _____		01 December 2022 (Date)	O.G. Print Claim(s) 1
			O.G. Print Figure NONE

U.S. Patent and Trademark Office

Part of Paper No.: 20221201

Docket No.: 37JD-199059-US13
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Gilead Sciences, Inc.

Application No.: 17/077,267

Confirmation No.: 4237

Filed: October 22, 2020

Art Unit: 1623

For: NUCLEOSIDE PHOSPHORAMIDATE
PRODRUGS

Examiner: Patrick T. Lewis

AMENDMENT AFTER FINAL ACTION UNDER 37 C.F.R. § 1.116

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

This Amendment is responsive to the Final Office Action dated September 22, 2022, concerning the above-referenced patent application. The Office set forth a three-month period to reply. Accordingly, this reply is timely filed before its due date of December 22, 2022. In response to the Action, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

117796 7590 12/07/2022
Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

EXAMINER

LEWIS, PATRICK T

ART UNIT

PAPER NUMBER

1623

DATE MAILED: 12/07/2022

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237

TITLE OF INVENTION: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	03/07/2023

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

117796 7590 12/07/2022
Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237

TITLE OF INVENTION: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1200	\$0.00	\$0.00	\$1200	03/07/2023

EXAMINER	ART UNIT	CLASS-SUBCLASS
LEWIS, PATRICK T	1623	514-023000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.563).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237
117796	7590	12/07/2022	EXAMINER	
Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626			LEWIS, PATRICK T	
			ART UNIT	PAPER NUMBER
			1623	
DATE MAILED: 12/07/2022				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b) (2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 17/077,267	Applicant(s) Du et al.	
	Examiner PATRICK T LEWIS	Art Unit 1623	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Amendment After Final dated 11/15/2022.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 13 and 17-18. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
Certified copies:
a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
* Certified copies not received: ____.

Applicant has **THREE MONTHS FROM THE "MAILING DATE"** of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in **ABANDONMENT** of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ **CORRECTED DRAWINGS** (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ **DEPOSIT OF and/or INFORMATION** about the deposit of **BIOLOGICAL MATERIAL** must be submitted. Note the attached Examiner's comment regarding **REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL**.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date <u>11152022</u> . 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____. 4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.	5. ☐ Examiner's Amendment/Comment 6. ☐ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
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/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	
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<i>Search Notes</i> 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Inventor, REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 (see attached)	04/07/2022	/PL/
Inventor, Updated REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 searches	09/16/2022	/PL/
Inventor, Updated REGISTRY, CAPLUS, MEDLINE, USPATFULL, USPAT2 searches	12/01/2022	/PL/

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	
--	--

<i>Search Notes</i> 	Application/Control No. 17/077,267	Applicant(s)/Patent Under Reexamination Du et al.
	Examiner PATRICK T LEWIS	Art Unit 1623

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
A61K	31/706, 31/7064, 31/7076, 31/7068, 45/06	12/01/2022	/PL/
C07D	417/14	12/01/2022	/PL/
C07H	17/02, 19/04, 19/06, 19/10, 19/20, 19/073	12/01/2022	/PL/
Y02A	50/30	12/01/2022	/PL/

/PATRICK T LEWIS/ Primary Examiner, Art Unit 1623	
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Substitute for form 1449/PTO INFORMATION DISCLOSURE STATEMENT BY APPLICANT <i>(Use as many sheets as necessary)</i>				Complete if Known	
				Application Number	17/077,267
				Filing Date	October 22, 2020
				First Named Inventor	Jinfa Du
				Art Unit	1623
				Examiner Name	Patrick T. Lewis
Sheet	1	of	1	Attorney Docket Number	37JD-199059-US13

U. S. PATENT DOCUMENTS					
Examiner Initials*	Cite No. ¹	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code ² (if known)			

FOREIGN PATENT DOCUMENTS						
Examiner Initials*	Cite No. ¹	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T ⁶
		Country Code ³ -Number ⁴ -Kind Code ⁵ (if known)				
		WO-2008104408	09-04-2008	K. U. LEUVEN RESEARCH & DEVELOPMENT		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No. ¹	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T ²
		Examination Report for Australian Application No. 2021202327 dated August 18, 2022. 9 pages	
		Office Action for Chinese Application No. 201811280509.0 dated October 13, 2022. 13 pages	

Examiner Signature	/PATRICK T LEWIS/	Date Considered	12/01/2022
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. ¹ Applicant's unique citation designation number (optional). ² See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. ³ Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). ⁴ For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. ⁵ Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. ⁶ Applicant is to place a check mark here if English language Translation is attached.

SMRH:4894-9330-1055.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /P.T.L./

PE2E SEARCH - Search History (Prior Art)

There are no Prior Art searches to show.

PE2E SEARCH - Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	British Equivalents	Time Stamp
N1	159261	(A61K31/706 OR A61K31/7064 OR A61K31/7076 OR A61K45/06 OR A61K31/7068 OR C07D417/14 OR C07H17/02 OR C07H19/04 OR C07H19/06 OR C07H19/10 OR C07H19/20 OR C07H19/073 OR Y02A50/30).cpc	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:19 AM
N2	7752	N1 AND phosphoramidate	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:19 AM
N3	3405	N2 AND (prodrug OR protide)	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:20 AM
N4	1147	N3 AND hcv	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:20 AM
N5	154	N4 AND 4'-C	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:20 AM
N6	154	N5 AND purine	(US-PGPUB; USPAT)	OR	ON	ON	2022/12/01 10:21 AM



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
 United States Patent and Trademark Office
 Address: COMMISSIONER FOR PATENTS
 P.O. Box 1450
 Alexandria, Virginia 22313-1450
 www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 4237

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.		
17/077,267	10/22/2020	514	1623	37JD-199059-US13		
APPLICANTS GILEAD PHARMASSET LLC, FOSTER CITY, CA; INVENTORS Jinfa Du, Redwood City, CA; Dhanapalan Nagarathnam, Bethany, CT; Michael Joseph Sofia, Doylestown, PA; Peiyuan Wang, San Mateo, CA;						
** CONTINUING DATA ***** This application is a CON of 16/817,318 03/12/2020 ABN which is a CON of 16/516,192 07/18/2019 ABN which is a CON of 16/169,878 10/24/2018 ABN which is a CON of 15/411,506 01/20/2017 PAT 10183037 which is a CON of 14/656,546 03/12/2015 PAT 9585906 which is a CON of 14/013,237 08/29/2013 PAT 9085573 which is a CON of 13/609,614 09/11/2012 PAT 8580765 which is a CON of 13/099,671 05/03/2011 PAT 8334270 which is a CON of 12/053,015 03/21/2008 PAT 7964580 which claims benefit of 60/982,309 10/24/2007 and claims benefit of 60/909,315 03/30/2007						
** FOREIGN APPLICATIONS ***** ** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 12/01/2020						
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☒ No Verified and Acknowledged <u>/PATRICK T LEWIS/</u> Examiner's Signature		☐ Met after Allowance Initials	STATE OR COUNTRY CA	SHEETS DRAWINGS 0	TOTAL CLAIMS 7	INDEPENDENT CLAIMS 1
ADDRESS Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626 UNITED STATES						
TITLE NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS						
FILING FEE RECEIVED 6180	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:			☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue)		

	☐ Other _____
	☐ Credit

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned 17/077,267
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		
<p>The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.</p> <p>This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.</p>			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
--------------------------	---

Inventor Information:

Inventor 1					Remove		
Legal Name							
Prefix	Given Name		Middle Name		Family Name		Suffix
	Jinfa				Du		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service							
City	Redwood City		State/Province	CA	Country of Residence	US	
Mailing Address of Inventor:							
Address 1		813 Bay Harbour Drive					
Address 2							
City	Redwood City		State/Province	CA			
Postal Code	94065		Country i	US			
Inventor 2					Remove		
Legal Name							
Prefix	Given Name		Middle Name		Family Name		Suffix
	Dhanapalan				Nagarathnam		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service							
City	Bethany		State/Province	CT	Country of Residence	US	
Mailing Address of Inventor:							
Address 1		52 Virginia Rail Drive					
Address 2							
City	Bethany		State/Province	CT			
Postal Code	06524		Country i	US			
Inventor 3					Remove		
Legal Name							
Prefix	Given Name		Middle Name		Family Name		Suffix
	Michael		Joseph		Sofia		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service							

Corrected 17/077,267 12/22/2022

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned 17/077,267
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

City	Doylestown	State/Province	PA	Country of Residence	US
Mailing Address of Inventor:					
Address 1		3066 Antler Drive			
Address 2					
City	Doylestown	State/Province	PA		
Postal Code	18902	Country i	US		
Inventor 4					Remove
Legal Name					
Prefix	Given Name	Middle Name	Family Name	Suffix	
	Pelyuan		Wang		
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service					
City	San Mateo	State/Province	CA	Country of Residence	US
Mailing Address of Inventor:					
Address 1		c/o Gilead Sciences, Inc.			
Address 2		333 Lakeside Drive			
City	Foster City	State/Province	CA		
Postal Code	94404	Country i	US		
All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the Add button.					Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence Information of this application.	
Customer Number	117796
Email Address	SVIPdocketing@sheppardmullin.com
	Add Email Remove Email

Application Information:

Title of the Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		
Attorney Docket Number	37JD-199059-US13	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

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Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned <u>17/077,267</u>
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

Request Not to Publish. I hereby request that the attached application not be published under

☐ 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number	117796		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
This Application <u>17/077,267</u>	Continuation of	16/817318	2020-03-12

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned 17/077,267
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Prior Application Status	Abandoned		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/817318	Continuation of	16/516192	2019-07-18		
Prior Application Status	Abandoned		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16/516192	Continuation of	16/169878	2018-10-24		
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
16/169878	Continuation of	15/411506	2017-01-20	10183037	2019-01-22
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15/411506	Continuation of	14/656546	2015-03-12	9585906	2017-03-07
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/656546	Continuation of	14/013237	2013-08-29	9085573	2015-07-21
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/013237	Continuation of	13/609614	2012-09-11	8580765	2013-11-12
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/609614	Continuation of	13/099671	2011-05-03	8334270	2012-12-18
Prior Application Status	Patented		Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/099671	Continuation of	12/053015	2008-03-21	7964580	2011-06-21
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
12/053015	Claims benefit of provisional	60/982309	2007-10-24		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
12/053015	Claims benefit of provisional	60/909315	2007-03-30		

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned <u>17/077,267</u>
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)¹ the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ^j (if applicable)	Remove

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

☐ NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned <u>17/077,267</u>
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned <u>17/077,267</u>
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

☒ Assignee
 ☐ Legal Representative under 35 U.S.C. 117
 ☐ Joint Inventor

☐ Person to whom the inventor is obligated to assign.
 ☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name ~~Gilead Pharmaceuticals LLC~~ Gilead Sciences, Inc.

Mailing Address Information For Applicant:

Address 1 ~~Gilead Sciences, Inc.~~ 333 Lakeside Drive

Address 2 ~~333 Lakeside Drive~~

City Foster City State/Province CA

Country US Postal Code 94404

Phone Number Fax Number

Email Address

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Corrected Application Data Sheet Application Data Sheet 37 CFR 1.76		Attorney Docket Number	37JD-199059-US13
		Application Number	Not Yet Assigned 17/077,267
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

Assignee 1				
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.				
If the Assignee or Non-Applicant Assignee is an Organization check here. ☐				
Prefix	Given Name	Middle Name	Family Name	Suffix
Mailing Address Information For Assignee including Non-Applicant Assignee:				
Address 1				
Address 2				
City		State/Province		
Country ¹		Postal Code		
Phone Number		Fax Number		
Email Address				
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.				

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).				
This Application Data Sheet must be signed by a patent practitioner if one or more of the applicants is a juristic entity (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, all joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of all joint inventor-applicants.				
See 37 CFR 1.4(d) for the manner of making signatures and certifications.				
Signature	/Joy Lynn Nemirow/		Date (YYYY-MM-DD)	2022-12-22
First Name	Joy Lynn	Last Name	Nemirow	Registration Number 67,163
Additional Signature may be generated within this form by selecting the Add button.				

Corrected Application Data Sheet		Attorney Docket Number	37JD-199059-US13
Application Data Sheet 37 CFR 1.76		Application Number	Not Yet Assigned <u>17/077,267</u>
Title of Invention	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: R46C.REQ

Document Description: Request under 37 CFR 1.46(c) to correct, update or change the applicant.

PTO/AIA/41 (04-15)

Approved for use through 05/31/2024. OMB 0651-0031

U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**REQUEST TO CORRECT OR UPDATE
THE NAME OF THE APPLICANT UNDER
37 CFR 1.46(c)(1), OR CHANGE THE
APPLICANT UNDER 37 CFR 1.46(c)(2)
(FOR USE ONLY IN APPLICATIONS FILED ON OR AFTER
SEPTEMBER 16, 2012)**

Application Number	17/077,267
Filing Date	October 22, 2020
First Named Inventor	Jinfa Du
Art Unit	1623
Examiner Name	Patrick T. Lewis
Practitioner Docket Number	37JD-199059-US13

**To: Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450**

Applicant hereby requests that the name of the applicant be corrected or updated under 37 CFR 1.46(c)(1), or that the applicant be changed under 37 CFR 1.46(c)(2), in the above-identified application. Requests under 37 CFR 1.46(c)(1) or (c)(2) cannot be submitted after payment of the issue fee or if the application has been patented.

Please check the applicable box(es) below.

☐ 1. This request is to **correct or update the name of the applicant (under 37 CFR 1.46(c)(1))** and includes:

☐ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) with the corrected or updated information shown with markings (e.g., underlining for insertions, strikethrough for deletions). A Corrected Web-based ADS may be used.

Note: Requests under 37 CFR 1.46(c)(1) may be filed to correct typographical errors in the name of the § 1.46 applicant, or for updating the name of the § 1.46 applicant (i.e., where there is no change in the applicant itself but just in the applicant's name). See the Manual of Patent Examining Procedure (MPEP) section 605.01.

☒ 2. This request is to **change the applicant (under 37 CFR 1.46(c)(2))** and includes:

☒ An application data sheet (ADS) in accordance with 37 CFR 1.76(c) that identifies the changes with proper markings (underlining for insertions and strikethrough for deletions). A Corrected Web-based ADS may be used.

☒ A Statement Under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent). See MPEP 325.

I am the

☐ applicant*

☐ attorney or agent of record

Registration number _____

☒ attorney or agent acting under 37 CFR 1.34

Registration number 67,163

Signature /Joy Lynn Nemirow/

Typed or printed name Joy Lynn Nemirow

Date December 22, 2022

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. *Juristic entities must be represented by a patent practitioner (See 37 CFR 1.31, applicable to any paper filed on or after September 16, 2012 that is presented on behalf of a juristic entity, regardless of application filing date). Submit multiple forms if more than one signature is required, see below**.

☒ ** Total of 1 forms are submitted.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0031. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. If filing this completed form by mail, send to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). <https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf>

Routine uses of the information in this record may include disclosure to: 1) law enforcement, in the event that the system of records indicates a violation or potential violation of law; 2) a Federal, state, local, or international agency, in response to its request; 3) a contractor of the USPTO having need for the information in order to perform a contract; 4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record; 5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record; 6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations; 7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals; 8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)); 9) the Office of Personnel Management (OPM) for personnel research purposes; and 9) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Additional Uses

Additional USPTO uses of the information in this record may include disclosure to: 1) the International Bureau of the World Intellectual Property Organization, if the record is related to an international application filed under the Patent Cooperation Treaty; 2) the public i) after publication of the application pursuant to 35 U.S.C. 122(b), ii) after issuance of a patent pursuant to 35 U.S.C. 151, iii) if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections, or an issued patent, or iv) without publication of the application or patent under the specific circumstances provided for by 37 CFR 1.14(a)(1)(v)-(vii); and/or 3) the National Archives and Records Administration, for inspection of records.

TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA/82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	17/077,267
Filing Date	October 22, 2020
First Named Inventor	Jinfa Du
Title	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
Art Unit	1623
Examiner Name	Patrick T. Lewis
Attorney Docket Number	37JD-199059-US13

SIGNATURE of Applicant or Patent Practitioner

Signature	/Joy Lynn Nemirow/	Date (Optional)	December 22, 2022
Name	Joy Lynn Nemirow	Registration Number	67,163
Title (if Applicant is a juristic entity)	Attorney for Applicant		
Applicant Name (if Applicant is a juristic entity)		Gilead Sciences, Inc.	

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.



*Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

117796

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name

Address

City

State

Zip

Country

Telephone

Email

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Gilead Sciences, Inc., 333 Lakeside Drive, Foster City, CA 94404

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	October 6, 2020 6:53:00 PM P
Name	96A2678F5319409... Mary J. Edwards		
Title	Sr. Associate General Counsel, IP		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: Gilead Sciences, Inc.Application No./Patent No.: 17/077,267 Filed/Issue Date: October 22, 2020Titled: NUCLEOSIDE PHOSPHORAMIDATE PRODRUGSGilead Sciences, Inc., a corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is ____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.
- B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Jinfa Du et al. To: Pharmasset, Inc.

The document was recorded in the United States Patent and Trademark Office at

Reel 062122, Frame 0886, or for which a copy thereof is attached.2. From: Pharmasset, Inc. To: Gilead Pharmasset LLC

The document was recorded in the United States Patent and Trademark Office at

Reel 062150, Frame 0476, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)3. From: Gilead Pharmasset LLC To: Gilead Sciences, Inc.The document was recorded in the United States Patent and Trademark Office at
Reel 058890, Frame 0229, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet(s).☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Joy Lynn Nemirow/
SignatureDecember 22, 2022
DateJoy Lynn Nemirow
Printed or Typed Name67,163
Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
17/077,267

RECEIPT DATE / TIME
12/22/2022 08:12:11 PM ET

ATTORNEY DOCKET #
37JD-199059-US13

Title of Invention

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	4237	FILED BY	Joannah Laluces
PATENT CENTER #	61345018	FILING DATE	10/22/2020
CUSTOMER #	117796	FIRST NAMED INVENTOR	Jinfa Du
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Joy Nemirow

Documents

TOTAL DOCUMENTS: 4

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
37JD-199059-US13_Request_to_Change_the_Applicant.pdf	2	Request under 37CFR1.46(c) to correct, update, change applicant	225 KB
37JD-199059-US13_Statement_under_37CFR373c.pdf	3	Assignee showing of ownership per 37 CFR 3.73	92 KB
37JD-199059-US13_Application_Data_Sheet.pdf	10	Application Data Sheet	1543 KB

Warning: This is not a USPTO supplied ADS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

37JD-199059- US13_Power_of_Attorney.pdf	3	Power of Attorney	673 KB
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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
37JD-199059- US13_Request_to_Change_the _Applicant.pdf	D760964EF8F6CEE9761FA31903503463235D8555D6CC023CA8 2C0739C05DE372A30B7BD6E93BDC73D3316356E14AA4CCD2 95A7ED2B4AFCEA6EF8A5B904E33AF6
37JD-199059- US13_Statement_under_37CF R373c.pdf	65C638E411A966752FD0BEE762AF179B28EA442EDCCDC2A1 DB411932696A42D695A21E5A3E547637C7C414EBB45F8954B4 03EB712BCA43151617E9484563C8F3
37JD-199059- US13_Application_Data_Sheet. pdf	A684373CBE0632DC115543961C778396AD87C3588C692B4A6 C777E06E4EDDC9F2138B68A3738F63EC4492CFCE51DDB7DE 651B80422237DBE18F4AD7713BBC65E
37JD-199059- US13_Power_of_Attorney.pdf	C785546F148A299AFC23E5EB6F45BAAF2233B712CAEE8FAE2 9F0FB357BE7337FA2E1CD5BCF6DD192002D2AA56F8A20E4E 4D6F1F29BBE149D24B08D020456171D

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
17/077,267	10/22/2020	1623	6180	37JD-199059-US13	7	1

CONFIRMATION NO. 4237
CORRECTED FILING RECEIPT

117796

Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626



CC00000137106438

Date Mailed: 01/03/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Jinfa Du, Redwood City, CA;
Dhanapalan Nagarathnam, Bethany, CT;
Michael Joseph Sofia, Doylestown, PA;
Peiyuan Wang, San Mateo, CA;

Applicant(s)

Gilead Sciences, Inc., Foster City, CA;

Power of Attorney: The patent practitioners associated with Customer Number 117796

Domestic Priority data as claimed by applicant

This application is a CON of 16/817,318 03/12/2020 ABN
which is a CON of 16/516,192 07/18/2019 ABN
which is a CON of 16/169,878 10/24/2018 ABN
which is a CON of 15/411,506 01/20/2017 PAT 10183037
which is a CON of 14/656,546 03/12/2015 PAT 9585906
which is a CON of 14/013,237 08/29/2013 PAT 9085573
which is a CON of 13/609,614 09/11/2012 PAT 8580765
which is a CON of 13/099,671 05/03/2011 PAT 8334270
which is a CON of 12/053,015 03/21/2008 PAT 7964580
which claims benefit of 60/982,309 10/24/2007
and claims benefit of 60/909,315 03/30/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 12/01/2020

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 17/077,267**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at <http://www.uspto.gov/web/offices/pac/doc/general/index.html>.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, <http://www.stopfakes.gov>. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13

CONFIRMATION NO. 4237

POA ACCEPTANCE LETTER



OC000000137106482

117796
Gilead Sciences, Inc.
c/o Sheppard Mullin Richter & Hampton LLP
650 Town Center Drive, 10th Floor
Costa Mesa, CA 92626

Date Mailed: 01/03/2023

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 12/22/2022.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/sleutchit/

Electronic Patent Application Fee Transmittal				
Application Number:		17077267		
Filing Date:		22-Oct-2020		
Title of Invention:		NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS		
First Named Inventor/Applicant Name:		Jinfa Du		
Filer:		Joy Lynn Bala Nemirow/Joannah Lalueces		
Attorney Docket Number:		37JD-199059-US13		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1200	1200
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1200

Electronic Acknowledgement Receipt	
EFS ID:	47310918
Application Number:	17077267
International Application Number:	
Confirmation Number:	4237
Title of Invention:	NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS
First Named Inventor/Applicant Name:	Jinfa Du
Customer Number:	117796
Filer:	Joy Lynn Bala Nemirow/Joannah Laluces
Filer Authorized By:	Joy Lynn Bala Nemirow
Attorney Docket Number:	37JD-199059-US13
Receipt Date:	03-JAN-2023
Filing Date:	22-OCT-2020
Time Stamp:	20:44:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	\$ 1200
RAM confirmation Number	E202313K44072075
Deposit Account	504561
Authorized User	Joannah Laluces
<p>The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:</p> <p>37 CFR 1.20 (Post Issuance fees)</p> <p>37 CFR 1.21 (Miscellaneous fees and charges)</p>	

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	62836	no	2
			e85882c47ed733fd5249e133c083ed1038a d0ea2		
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	40327	no	2
			0cd710fdda8ea2b0e6a3193b9a353bab4dc 44162		
Warnings:					
Information:					
Total Files Size (in bytes):			103163		
<p>This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.</p> <p><u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.</p> <p><u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.</p> <p><u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.</p>					

Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
17077267	22-Oct-2020	Jinfa Du	37JD-199059-US13	4237

TITLE OF INVENTION :

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1623	023000	PATRICK LEWIS
Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
\$1200	\$0	\$1200	07-Mar-2023	\$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
117796 Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa CA 92626 UNITED STATES (650) 815-2600 SheppardMullin_Pair@firsttofile.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status**Change in Entity Status**

Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.

Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.



Applicant asserting small entity status. See 37 CFR 1.27.

Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.



Applicant changing to regular undiscounted fee status.

Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.



WEB IFEE 1.0

Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:☒ Issue Fee

I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____If in addition to the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency or credit any overpayment, to Deposit Account Number ⁵⁰⁻⁴⁵⁶¹_____.**The issue fee must be submitted with this form. If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.****4.Firm and/or Attorney Names To Be Printed****NOTE: If no name is listed, no name will be printed**

For printing on the patent front page, list to be displayed as entered

1. SHEPPARD MULLIN RICHTER & HAMPTON LLP

2.

3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
Gilead Sciences, Inc.	Foster City	CALIFORNIA	UNITED STATES	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Joy Lynn Nemirow/	Date	01-03-2023
Name	Joy Lynn Nemirow	Registration Number	67163

WEB IFEE 1.0



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
17/077,267	10/22/2020	Jinfa Du	37JD-199059-US13	4237
117796 7590 01/20/2023 Gilead Sciences, Inc. c/o Sheppard Mullin Richter & Hampton LLP 650 Town Center Drive, 10th Floor Costa Mesa, CA 92626			EXAMINER LEWIS, PATRICK T	
			ART UNIT 1623	PAPER NUMBER
			NOTIFICATION DATE 01/20/2023	DELIVERY MODE ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

SheppardMullin_Pair@firsttofile.com
ipdocketing@gilead.com
svipdocketing@sheppardmullin.com



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 17077267
Applicant : Du
Filing Date : 10/22/2020
Date Mailed : 01/20/2023

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

*A copy of this notice **MUST** be returned with the reply. Please address response to
"Mail Stop Issue Fee, Commissioner for Patents,
P.O. Box 1450, Alexandria, VA 22313-1450".*

/June Hope/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 17077267

**IDENTIFICATION OF APPLICATION DEFICIENCIES
IN APPLICATION FILED ON OR AFTER SEPTEMBER 16, 2012**

- ☒ Applicant must provide legible text for the following item(s).
- ☒ Specification filed 10/22/2020, page(s) (see below).
- ☐ Claims filed , claim(s) .
- ☐ Other: .
- ☐ Applicant must provide missing information on the following page(s) of the specification by amending the specification to add the missing text. No new matter may be added.
Page/line no(s).
- ☐ The specification refers to one or more applications by attorney docket number and does not show the U.S. application number(s). Applicant must supply the U.S. application number in place of each attorney docket number.
Page/line no(s).
- ☐ Applicant must provide an Abstract of the Disclosure.
- ☐ The Application Data Sheet (ADS dated) does not supply the inventor's city and/or does not supply the inventor's U.S. state and/or does not supply the inventor's country. Applicant must submit a signed, in accordance with 37 CFR 1.76(e) and 1.33(b), application data sheet that corrects this deficiency. To be in compliance with 37 CFR 1.76, the corrected application data sheet must identify the information being changed by using underlining for additions and strikethroughs or brackets for deletions.
- ☒ Other: The following Spec pages contain overlapping and/or obscured data: Pages 116, 133, 151, 169, 186, 204, 221, 238, 256, 273, 291, 308, 326, 343, 360, 378, 395, 413, 430, 447, 465, 482, 499, 517, 534, 551, 568, 585, 602, 620 and 637.

The response to this notice should contain only amended papers, as the waiver of 37 CFR 1.312 is limited to corrections of documents specifically requested in the notice.

NUCLEOSIDE PHOSPHORAMIDATE PRODRUGS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application No. 16/817,318, filed March 12, 2020, now abandoned, which is a continuation of U.S. Patent Application No. 16/516,192, filed July 18, 2019, now abandoned, which is a continuation of U.S. Patent Application No. 16/169,878, filed October 24, 2018, now abandoned, which is a continuation of U.S. Patent Application No. 15/411,506, filed January 20, 2017, now U.S. Patent No. 10,183,037, which is a continuation of U.S. Patent Application No. 14/656,546, filed March 12, 2015, now U.S. Patent No. 9,585,906, which is a continuation of U.S. Patent Application No. 14/013,237, filed August 29, 2013, now U.S. Patent No. 9,085,573, which is a continuation of U.S. Patent Application No. 13/609,614, filed September 11, 2012, now U.S. Patent No. 8,580,765, which is a continuation of U.S. Patent Application No. 13/099,671, filed May 3, 2011, now U.S. Patent No. 8,334,270, which is a continuation of U.S. Patent Application No. 12/053,015, filed March 21, 2008, now U.S. Patent No. 7,964,580, which claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Application Nos. 60/909,315, filed March 30, 2007, and 60/982,309, filed October 24, 2007, all of which are hereby incorporated by reference in their entireties.

Sequence Listing

The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety.

Field of Invention

The present invention pertains to nucleoside phosphoramidates and their use as agents for treating viral diseases. These compounds are inhibitors of RNA-dependent RNA viral replication and are useful as inhibitors of HCV NS5B polymerase, as

5 inhibitors of HCV replication and for treatment of hepatitis C infection in mammals. The invention provides novel chemical compounds, and the use of these compounds alone or in combination with other antiviral agents for treating HCV infection.

Background

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic

10 liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals, estimated to be 2-15% of the world's population. There are an estimated 4.5 million infected people in the United States alone, according to the U.S. Center for Disease Control. According to the World Health Organization, there are more than 200 million infected individuals worldwide, with at least 3 to 4 million people being

15 infected each year. Once infected, about 20% of people clear the virus, but the rest can harbor HCV the rest of their lives. Ten to twenty percent of chronically infected individuals eventually develop liver-destroying cirrhosis or cancer. The viral disease is transmitted parenterally by contaminated blood and blood products, contaminated needles, or sexually and vertically from infected mothers or carrier mothers to their

20 offspring. Current treatments for HCV infection, which are restricted to immunotherapy with recombinant interferon- α alone or in combination with the nucleoside analog ribavirin, are of limited clinical benefit. Moreover, there is no established vaccine for

HCV. Consequently, there is an urgent need for improved therapeutic agents that effectively combat chronic HCV infection.

The HCV virion is an enveloped positive-strand RNA virus with a single oligoribonucleotide genomic sequence of about 9600 bases which encodes a polyprotein of about 3,010 amino acids. The protein products of the HCV gene consist of the structural proteins C, E1, and E2, and the non-structural proteins NS2, NS3, NS4A and NS4B, and NS5A and NS5B. The nonstructural (NS) proteins are believed to provide the catalytic machinery for viral replication. The NS3 protease releases NS5B, the RNA-dependent RNA polymerase from the polyprotein chain. HCV NS5B polymerase is required for the synthesis of a double-stranded RNA from a single-stranded viral RNA that serves as a template in the replication cycle of HCV. Therefore, NS5B polymerase is considered to be an essential component in the HCV replication complex (K. Ishi, et al, *Heptology*, 1999, 29: 1227-1235; V. Lohmann, et al., *Virology*, 1998, 249: 108-118). Inhibition of HCV NS5B polymerase prevents formation of the double-stranded HCV RNA and therefore constitutes an attractive approach to the development of HCV-specific antiviral therapies.

HCV belongs to a much larger family of viruses that share many common features.

Flaviviridae Viruses

The Flaviviridae family of viruses comprises at least three distinct genera: *pestiviruses*, which cause disease in cattle and pigs; *flaviviruses*, which are the primary cause of diseases such as dengue fever and yellow fever; and *hepaciviruses*, whose sole