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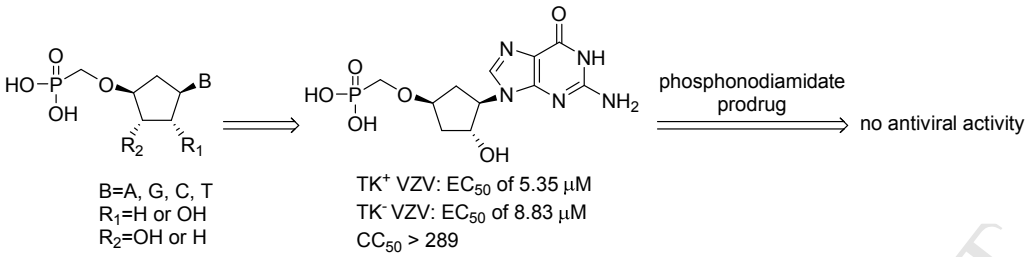
Graphical Abstract



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Synthesis and Antiviral Evaluation of Cyclopentyl Nucleoside Phosphonates

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ABSTRACT

The synthesis of both 2′-hydroxy-3′-deoxy and 2′-deoxy-3′-hydroxy cyclopentyl nucleoside phosphonates with the natural nucleobases adenine, thymine, cytosine and guanine from a single precursor has been performed. The guanine containing analogues showed antiviral activity. Especially the 3′-deoxy congener **23** was active, displaying an EC_{50} of 5.35 μM against TK^+ VZV strain and an EC_{50} of 8.83 μM against TK^- VZV strain, besides lacking cytotoxicity. However, the application of phosphonodiamidate prodrug strategy did not lead to a boost in antiviral activity.

Keywords

Carbocyclic nucleoside, nucleoside phosphonate, antiviral, prodrug.

1. Introduction

The synthesis of modified nucleosides is an ongoing research theme in antiviral drug discovery. A prominent class of structurally modified nucleoside analogues are carbocyclic nucleosides, in which the oxygen of the furanose ring of the natural nucleosides is replaced by a methylene group [1,2]. The absence of the labile glycosidic bond makes carbocyclic nucleosides chemically and enzymatically more stable than their natural counterparts. A number of biologically active carbocyclic nucleosides have been isolated from natural sources. Examples include Aristeromycin and Neplanocin A (Figure 1), which are both carbocyclic adenosine analogues [3], that act as inhibitors of *S*-adenosyl-L-homocysteine (SAH) hydrolase and exhibit broad spectrum antiviral activity but with concomitant cytotoxicity on the host cell [4,5]. It inspired medicinal chemists to synthesize novel carbocyclic nucleosides as selective antiviral agents [6,7]. It led to the marketing approval of Abacavir [8] and Entecavir [9] as drugs for the treatment of HIV- and HBV-infected patients, respectively.

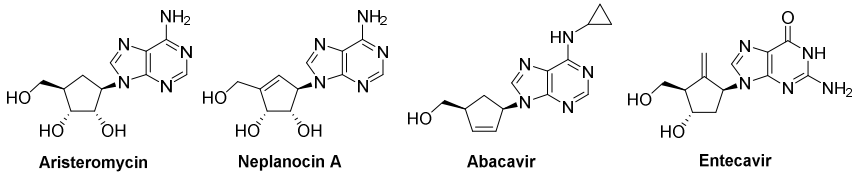


Figure 1. Examples of biologically active carbocyclic nucleosides.

The antiviral activity of these nucleoside analogues depends upon their intracellular metabolism within virus-infected cells to form sequentially the mono-, di- and triphosphates. Nucleoside triphosphates are the pharmacologically active species, as they are incorporated into a growing DNA or RNA strand resulting in chain termination. The first phosphorylation step is usually the rate-limiting step in the conversion to the nucleoside-5′-triphosphate. The synthesis of a nucleoside phosphonate, in which the P-O-CH_2 group of the naturally occurring nucleoside monophosphate is replaced by a P-CH_2-O moiety, allows the first phosphorylation step to be bypassed. Nucleoside phosphonates are essentially nucleoside monophosphate analogues, having the advantage of being chemically and metabolically stable. The success of this motif is due to the fact that it is isopolar and isosteric with the phosphate group [10]. Hence, nucleoside phosphonates can undergo enzymatic phosphorylations furnishing the phosphonate diphosphates, which act as analogues of the natural nucleoside triphosphates.

Despite the promising characteristics of carbocyclic nucleosides and nucleoside phosphonates as antivirals, carbocyclic nucleoside phosphonates, combining the two aforementioned approaches, have been described to a much lesser extent (Figure 2). A phosphonate analogue of carbocyclic brivudine (compound **1**) lacked antiviral activity against herpes viruses [11]. A carbocyclic nucleoside phosphonate bearing a 4′-ethynyl group (compound **2**) displayed *in vitro* anti-HIV activity [12]. 2′-Deoxyguanosine-5′-phosphonate (compound **3**) was endowed with cytotoxic activity against HEp-2 cells [13].

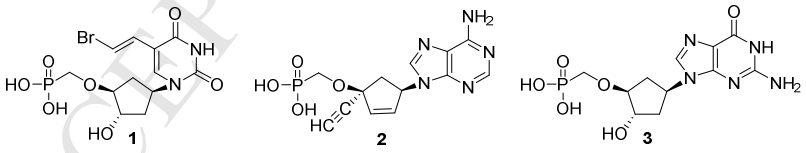
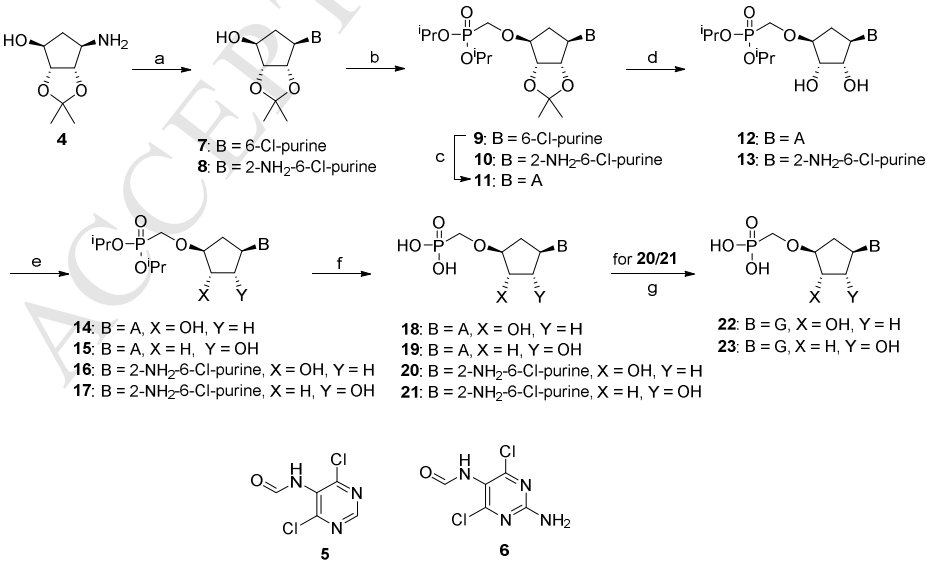


Figure 2. Known carbocyclic nucleoside phosphonates.

As only a limited number of carbocyclic nucleoside phosphonates are known, we embarked on the synthesis of a series of 2′-deoxy-3′-hydroxy and 2′-hydroxy-3′-deoxy carbocyclic nucleoside phosphonates with the natural nucleobases adenine, thymine, cytosine and guanine. These compounds were evaluated for antiviral activity against different DNA viruses from the herpesvirus family.

2. Chemistry

2.1. Synthesis of cyclopentyl nucleoside phosphonates with adenine and guanine bases. The synthesis of both series of compounds is shown in Scheme 1. Reaction of the commercially available starting material **4** with 4,6-dichloro-5-formamidopyrimidine **5** and 2-amino-4,6-dichloro-5-formamidopyrimidine **6**, afforded the 6-chloro-purine and 2-amino-6-chloro-purine containing nucleosides **7** and **8**, respectively [14]. Alkylation of the secondary hydroxyl group under basic conditions afforded the protected nucleoside phosphonates **9** and **10**. Substitution of the chlorine of compound **9** by an amino group was achieved by treatment of compound **9** with a 7N NH_3 solution in MeOH, yielding the adenine derivative **11**. Acidic deprotection of the isopropylidene moiety of **10** and **11** afforded compounds **12** and **13**. Reductive removal of a hydroxyl group under standard Barton deoxygenation conditions gave a mixture of compounds **14**/**15** and **16**/**17** in a ratio of 5:3. These regioisomeric mixtures were used for the following step without separation. Lewis acid-mediated cleavage of the phosphonate esters gave the nucleoside phosphonic acids **18**/**19** and **20**/**21**. At this stage of the synthesis, isomers **18** and **19** were separated by reversed phase HPLC, whereas the 2-amino-6-chloropurine moiety of the mixture **20**/**21** was converted to the guanine base by refluxing **20/21** in a 4N sodium hydroxide solution, affording the guanine cyclopentyl phosphonates **22/23.** The 2′-deoxy derivative **22** and the 3′-deoxy analogue **23** were successfully separated by reversed phase HPLC. The assignment of the correct regiochemistry of isomers **18**/**19** and **22**/**23** was based on H-H COSY NMR spectroscopy. As a representative example, the key COSY correlations for compounds **18** and **19** are shown in Figure 3. The observation of COSY correlations of H-1′ with H-2a′ and H-2b′, and H-4′ with H-3′ allowed to identify compound **18** as the 2′-deoxy analogue. Correlations of H-1′ with H-2′ and H-4′ with H-3a′ and H-3b′ allowed to assign the 3′-deoxy regiochemistry to compound **19**.



Scheme 1. Synthesis of adenine and guanine containing cyclopentyl nucleoside phosphonates. *Reagents and conditions:* (a) **5** or **6**, DIPEA, *n*-butanol, overnight, 64% for **7** and 66% for **8**; (b) $(i\text{PrO})_2\text{POCH}_2\text{OTf}$, NaH, THF, 0 °C to rt, 20 min, 92% for **9** and 76% for **10**; (c) 7N NH_3 in MeOH, 65 °C, overnight, 70%; (d) PTSA, MeOH, 5 h, 86% for **12** and 80% for **13**; (e) (1) TCDI, DMAP, CH_2Cl_2, overnight; (2) AIBN, Bu_3SnH, toluene, reflux, 20 min, 70% for 2 steps (**14**:**15** = ratio 5:3; **16**:**17** = ratio 5:3); (f) TMSBr, CH_3CN, rt, overnight, 65–80%; (g) for **20**/**21**, 4N NaOH, reflux, 4 h, 77%.

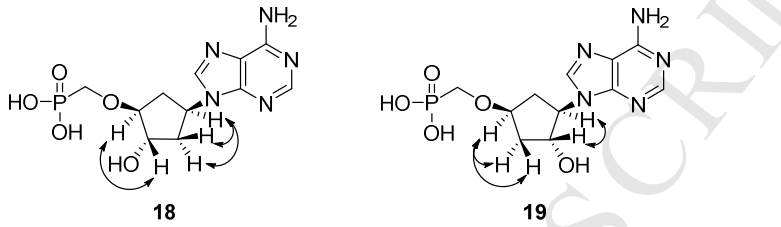
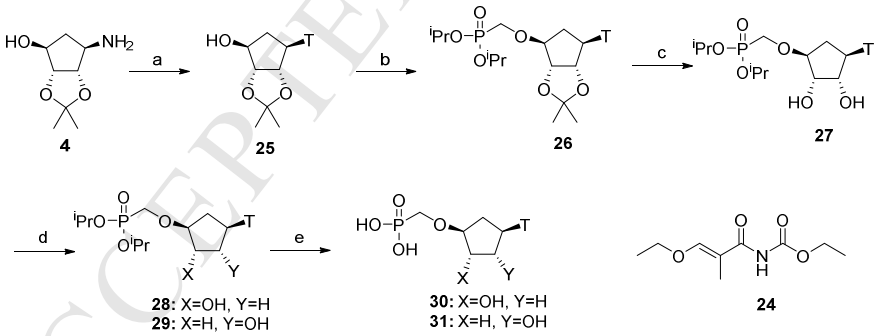


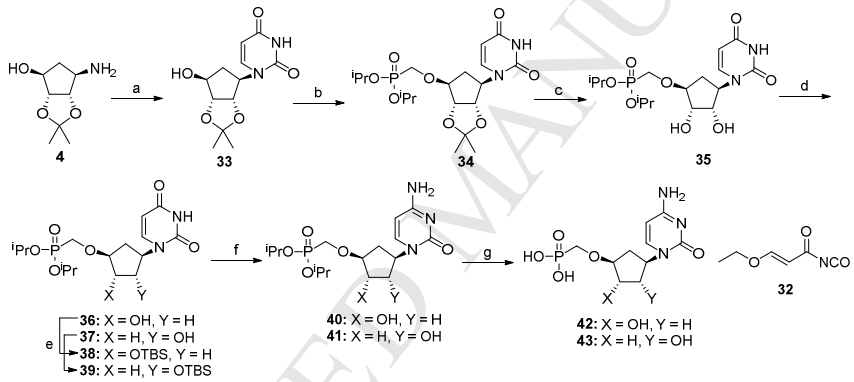
Figure 3. H-H COSY correlations of compounds **18** and **19**.

2.2. Synthesis of cyclopentyl nucleoside phosphonates with a thymine base. In the first step, reaction of compound **4** with ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl] carbamate **24**, was followed by an intramolecular cyclization in aqueous ammonia yielding thymine derivative **25** (Scheme 2). Introduction of the phosphonate moiety, reductive removal of the hydroxyl groups and final deprotection proceeded analogously as in Scheme 1, affording a mixture of the 2′-deoxy and 3′-deoxy thymine derivatives that were separated by RP-HPLC, yielding pure compounds **30** and **31**.



Scheme 2. Synthesis of thymine containing cyclopentyl nucleoside phosphonates. *Reagents and conditions:* (a) (1) **24**, dioxane, 100 °C, 3 h; (2) aq. NH_4OH, 90 °C, overnight, 85%; (b) $(i\text{PrO})_2\text{POCH}_2\text{OTs}$, NaH, THF, 0 °C to rt, 10 h, 84%; (c) PTSA, MeOH, 3 h, 85%; (d) (1) TCDI, DMAP, CH_2Cl_2, overnight; (2) Bu_3SnH, AIBN, toluene, reflux, 20 min, 85% for 2 steps (**28**:**29** = ratio 5:3); (e) TMSBr, CH_3CN, rt, overnight, 85%.

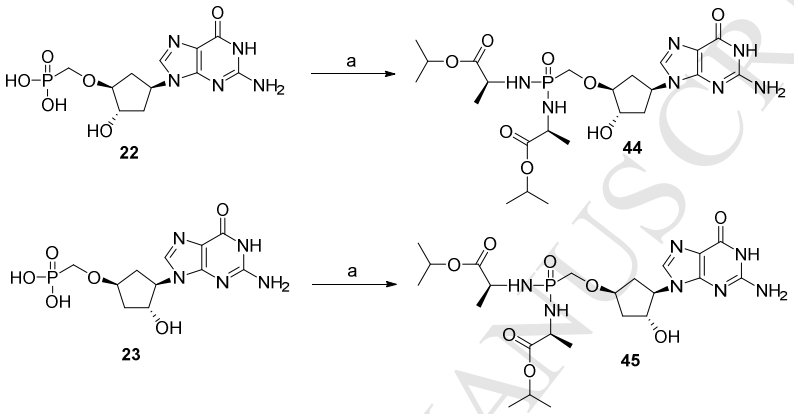
2.3. Synthesis of cyclopentyl nucleoside phosphonates with a cytosine base. Similarly as for the thymidine congeners, the formation of the cytosine nucleobase is also a two-step, one-pot reaction that included the addition of amine **4** to intermediate (*E*)-3-ethoxyacryloyl isocyanate **32** and a subsequent cyclization with aq. ammonia furnishing uridine analogue **33** (Scheme 3). Insertion of the phosphonate functionality and acidic cleavage of the acetonide protecting group yielded compound **35**. Deoxygenation of compound **35** using standard Barton deoxygenation reaction conditions gave a mixture of compounds **36** and **37,** which was used for further reactions as a regioisomeric mixture. Prior to conversion of uracil to cytosine, the 3′-hydroxyl (of compound **36**) or the 2′-hydroxyl (of compound **37**) were protected as a *tert*-butyldimethylsilyl ether. The resulting derivatives **38** and **39** were then treated with TIPSCl, followed by treatment with an aqueous ammonia solution, yielding the protected cytosine derivatives **40** and **41**. Deprotection of the silyl group and cleavage of phosphonate esters gave access to the nucleoside phosphonic acids **42** and **43**, that were separated by reversed phase HPLC.



Scheme 3. Synthesis of cytosine containing cyclopentyl nucleoside phosphonates. *Reagents and conditions:* (a) (1) **32**, DMF, −15 to 0 °C, overnight; (2) aq. NH_4OH, 90 °C, overnight, 80%; (b) $(iPrO)_2POCH_2OTs$, NaH, THF, 0 to rt, 10 h, 92%; (c) PTSA, MeOH, 3 h, 85%; (d) (1) TCDI, DMAP, CH_2Cl_2, overnight; (2) Bu_3SnH, AIBN, toluene, reflux, 20 min, 79% for 2 steps (**36**:**37** = ratio 5:3); (e) TBSCl, imidazole, DMF, rt, overnight, 80%; (f) (1) TIPSCl, DMAP, Et_3N, CH_3CN, rt, overnight; (2) aq. NH_4OH, 0.5 h, 70%; (3) $Et_3N \cdot 3HF$, THF, rt, overnight, 80%; (g) TMSBr, CH_3CN, rt, overnight, 79%.

2.4. Synthesis of the prodrugs of cyclopentyl nucleoside phosphonates containing a guanine base. Because of the promising antiviral activity of the parent nucleoside phosphonates **22** and **23**, they were converted to their corresponding prodrugs. Initial attempts were focused on the synthesis of phenoxyphosphonoamidate prodrugs with L-alanine isopropylester as amino acid motif. However, applying standard reaction conditions [15] with a mixture of phenol and L-alanine isopropyl ester HCl and using 2,2′-dithiodipyridine and triphenylphosphine as activating agents yielded the desired compounds in very low yield. This was due to the low solubility of phosphonates **22** and **23** in pyridine as well as to the

concomitant formation of the corresponding phosphonodiamidates. Therefore, we switched to the synthesis of phosphonodiamidate rather than phenoxyphosphonoamidates (Scheme 4). In addition, phenoxyphosphonoamidate prodrugs exist as diasteromeric mixtures due to the chirality of the phosphorus atom, while phosphonodiamidates are isolated as single isomer. The phosphonodiamidate prodrugs were prepared from the parent phosphonates (compounds **22** and **23**) and L-alanine isopropyl ester HCl using 2,2′-dithiodipyridine and triphenylphosphine as activating agents affording the desired prodrugs **44** and **45** in moderate yields.



Scheme 4. Synthesis of cyclopentyl phosphonodiamidate prodrugs with a guanine base. *Reagents and conditions:* (a) L-alanine isopropyl ester HCl salt, Et_3N, PPh_3, pyridine, 60 °C, overnight, 32–36%.

3. Results and discussion

All cyclopentyl nucleoside phosphonates were evaluated for antiviral activity against different DNA viruses from the Herpesviridae family. These included varicella-zoster virus (VZV, strains TK^+ and TK^-), human cytomegalovirus (HCMV, strains AD-169 and Davis) and herpes simplex virus 1 and 2 (HSV-1 KOS, HSV-2 G, HSV-1 KOS ACV^r). The antiviral assays are based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts. Antiviral activity is expressed as the EC_{50} or compound concentration required reducing virus-induced cytopathogenicity or viral plaque formation by 50%. At the same time, the cytostatic activity of the compounds was also investigated. The cytostatic concentration is calculated as the CC_{50}, or the compound concentration required to reduce cell proliferation by 50% relative to the number of cells in the untreated controls. Alternatively, cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology. As can be derived from the data in Table **1**, the adenine (compounds **18**/**19**) and the cytosine (compounds **42**/**43**) containing congeners were completely devoid of antiviral activity. The 2′-deoxy thymidine analogue (compound **30**) displayed weak antiviral activity, whereas the 3′-deoxy thymidine

derivative (compound **31**) completely lacked antiviral activity. The most promising antiviral activity within the carbocyclic nucleoside phosphonates was found within the guanosine series. The 2′-deoxy analogue (compound **22**) showed weak antiviral activity against VZV, HCMV and HSV, with EC_{50} values in the 8-34 µM range. The 3′-deoxy guanosine analogue (compound **23**) was especially active against VZV (EC_{50}'s in the range of 5-8 µM), whereas its activity against HCMV and HSV was less pronounced. The high polarity of the nucleoside phosphonates hampers their cellular permeability, which has a negative impact on the antiviral activity. Phosphonoamidate prodrugs are well-known to increase the antiviral activity of nucleoside phosphonates against HIV and HBV [16-19]. We applied this strategy to compounds **22** and **23** by the synthesis of the corresponding phosphonodiamidate prodrugs **44** and **45**, respectively, to evaluate the phosphonoamidate prodrug strategy against VZV, HCMV and HSV. To our surprise, both prodrugs completely lacked antiviral activity. This suggested that the diamidate prodrugs are not recognized by specific cellular enzymes in HEL cells, which are necessary to release the biologically active nucleoside phosphonate.

Table 1. Antiviral activity and cytotoxicity of cyclopentyl nucleoside phosphonates and their prodrugs against HSV, HCMV and VZV in HEL cells

Compound	Antiviral activity EC_{50}[a] (µM)							Cytotoxicity (µM)	
	VZV		HCMV		HSV			Cell morphology (MCC)[b]	Cell growth (CC_{50})[c]
	TK^+ VZV strain	TK^- VZV strain	AD-169 strain	Davis strain	HSV-1 KOS strain	HSV-2 G strain	HSV-1 KOS ACV^r strain	HEL	HEL
18	258	79	>303	>303	>303	>303	>303	>303	ND[d]
19	>303	>303	>303	>303	>303	132.04	161.44	>303	ND[d]
22	17.14	**8.38**	18.73	14.74	22.72	33.94	14.10	>289	>289
23	**5.35**	**8.83**	14.97	37.98	**7.57**	57.92	99.05	>289	>289
30	23.14	5.73	13.98	25.92	117.32	92.27	9.89	>247	69.42
31	>247	>247	>247	>247	>247	>247	>247	>247	ND[d]
42	>327	>327	>327	>327	>327	>327	>327	>327	ND[d]
43	>327	>327	>327	>327	>327	>327	>327	>327	ND[d]
44	34.99	29.79	24.65	13.54	34.99	85.55	34.99	>175	>175
45	66.60	>175	>175	>175	>175	>175	>175	>175	>175
Acyclovir	3.37	14.12	ND[d]	ND[d]	0.30	0.29	>88	>444	>444
Brivudin	0.021	3.39	ND[d]	ND[d]	0.045	>30	>30	>300	>300
Ganciclovir	ND[d]	ND[d]	6.46	4.83	0.045	0.019	3.91	>391	>391
Cidofovir	ND[d]	ND[d]	0.79	0.98	3.18	2.27	1.75	>358	>358

[a]Effective concentration required to reduce virus plaque formation by 50%. [b]Minimum cytotoxic concentration that

causes a microscopically detectable alteration of cell morphology. [c]Cytotoxic concentration required to reduce cell growth by 50%. [d]Not determined.

4. Conclusion

In this manuscript, the synthesis of eight cyclopentyl nucleoside phosphonates with a adenine, thymine, cytosine and guanine base was described. Both 2′-deoxy and 3′-deoxy analogues were prepared. As the guanosine congeners showed limited antiviral activity, the synthesis of their corresponding phosphonodiamidate prodrugs was also effected. Both prodrugs were completely devoid of antiviral activity, which is a rare exception to the general accepted theory that synthesis of phosphonoamidate prodrugs of nucleoside analogues leads to an increase of antiviral activity. This is most likely due to the fact that these phosphonoamidates are intracellularly not metabolized to the parent nucleoside phosphonates.

5. Experimental section

5.1. General information

Moisture sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. All reagents and solvents were obtained from commercial sources and used as received. Meting points were determined on a Buchi 530 melting point apparatus and were uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a 300, 500 or 600 MHz Bruker Avance spectrometer and using tetramethylsilane as an internal standard or referenced to the residual solvent signal and 85% H_3PO_4 for ^{31}P NMR. 2D NMR (H-COSY, HSQC, and HMBC) was used for the assignment of proton and carbon signals of intermediates and final compounds. High-resolution mass spectra (HRMS) were recorded on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL min^{-1}, and spectra were obtained in positive or negative ionization mode with a resolution of 15 000 (fwhm) using leucine enkephalin as a lock mass. Column chromatography was carried out on silica gel 60 Å, 0.035–0.070 mm (Acros Organics). Preparative high performance liquid chromatography (HPLC) purifications were performed on a Phenomenex Gemini 110A column (C18, 10 μm, 21.2 mm × 250 mm) using CH_3CN/0.05 M TEAB buffer or H_2O/CH_3CN as eluent gradient. Purities of all of the tested compounds were above 95% by HPLC analysis.

*5.1.1. 9-[(1′R,2′S,3′R,4′S)-4′-Hydroxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]-6-chloro-9-H-purine (**7**)* [20]. To a solution of compound **4** (0.35 g, 2,02 mmol) and 4,6-dichloro-5-formamidopyrimidine (0.422 mg, 2.22 mmol) in *n*-butanol (20 mL) was added DIPEA (1.41 mL, 8.08 mmol). The mixture was refluxed at 120 °C overnight. The solvent was removed under reduced pressure, and the residue was

purified by column chromatography (1:1, hexane/EtOAc) to afford compound **7** (0.40 g, 64% yield) as a yellowish amorphous solid. m.p. 134-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 1H, H-2), 8.58 (s, 1H, H-8), 5.13 (d, J = 9.0 Hz, 1H, H-1′), 4.93 (d, J = 5.5 Hz, 1H, H-2′), 4.75 (d, J = 5.4 Hz, 1H, H-3′), 4.58 (d, J = 4.8 Hz, 1H, H-4′), 2.93-2.85 (m, 1H, H-5a′), 2.29 (d, J = 15.5 Hz, 1H, H-5b′), 1.54 (s, 3H, CH_3), 1.32 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7 (C-2), 151.4 (C-4), 151.0 (C-6), 145.7 (C-8), 131.6 (C-5), 111.8 [C(CH_3)$_2$], 87.0 (C-3′), 86.2 (C-2′), 76.1 (C-4′), 62.5 (C-1′), 36.9 (C-5′), 26.7 (CH_3), 24.2 (CH_3) ppm. HRMS: $[M+H]^+$ calcd for $C_{13}H_{16}N_4O_3Cl$, 311.0905; found, 311.0903.

*5.1.2. 9-[(1′R,2′S,3′R,4′S)-4′-Hydroxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]-2-amino-6-chloro-9-H-purine (**8**).* This compound was prepared as described for **7**. Obtained from compound **4** (0.50 g, 2.89 mmol), 2-amino-4,6-dichloro-5-formamidopyrimidine (0.71 g, 3.46 mmol) and DIPEA (2.01 mL, 11.55 mmol) as a yellowish amorphous solid (0.62 g, 66% yield). m.p. 137-139 °C. ^{1}H NMR (500 MHz, DMSO): δ 8.25 (s, 1H, H-8), 6.92 (brs, 2H, NH_2), 5.50 (d, J = 3.4 Hz, 1H, OH), 4.92 (dd, J = 1.8, 6.1 Hz, 1H, H-2′), 4.73-4.70 (m, 1H, H-1′), 4.56 (d, J = 6.1 Hz, 1H, H-3′), 4.17 (m, 1H, H-4′), 2.50 (1H overlap H-5′), 2.11-2.07 (m, 1H, H-5′), 1.41 (s, 3H, CH_3), 1.23 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, DMSO): δ 159.7 (C-2), 154.0 (C-4), 149.4 (C-6), 142.3 (C-8), 123.3 (C-5), 110.8 [C(CH_3)$_2$], 86.3 (C-3′), 84.5 (C-2′), 74.8 (C-4′), 59.7 (C-1′), 36.9 (C-5′), 26.7 (CH_3), 24.4 (CH_3) ppm. HRMS: $[M+H]^+$ calcd for $C_{13}H_{17}N_5O_3Cl$, 326.1014; found, 326.1011.

*5.1.3. 9-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]-6-chloro-9-H-purine (**9**).* To a solution of compound **7** (0.40 g, 1.29 mmol) and triflate diisopropylphosphonomethanol (0.55 g, 1.67 mmol) in anhydrous THF (10 mL) was added sodium hydride (60% in mineral oil, 0.062 g, 1.54 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature. It was quenched with sat. aq. NH_4Cl and was concentrated. The residue was partitioned between H_2O and EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (30:1, DCM/MeOH) to afford compound **9** (0.58 g, 92% yield) as a white amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.77 (s, 1H, H-2), 8.47 (s, 1H, H-8), 5.13 (d, J = 7.0 Hz, 1H, H-1′), 4.93 (d, J = 6.0 Hz, 1H, H-2′), 4.81 (d, J = 6.0 Hz, 1H, H-3′), 4.79-4.70 [m, 2H, CH(CH_3)$_2$], 4.21 (d, J = 3.1 Hz, 1H, H-4′), 3.90-3.74 (m, 2H, PCH_2), 2.86-2.77 (m, 1H, H-5′), 2.39 (d, J = 15.3 Hz, 1H, H-5′), 1.53 (s, 3H, CH_3), 1.36-1.29 (m, 15H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9 (C-6), 151.8 (C-2), 150.9 (C-4), 144.8 (C-8), 131.6 (C-5), 112.2 [C(CH_3)$_2$], 86.2 (d, $^{3}J_{P,C}$ = 10.6 Hz, C-4′), 85.3 (C-2′), 83.4 (C-3′), 71.4 [CH(CH_3)$_2$], 71.3 [CH(CH_3)$_2$], 64.5 (d, $^{1}J_{P,C}$ = 168.6 Hz, PCH$_2$), 60.9 (C-1′), 35.0 (C-5′), 26.5 (CH_3), 24.1(CH_3), 24.0 (CH_3), 23.9 (CH_3), 23.9 (CH_3) ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ 18.1 ppm. HRMS: $[M+H]^+$ calcd for $C_{20}H_{31}N_4O_6ClP$, 489.1664; found, 489.1661.

*5.1.4. 9-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]-2-amino-6-chloro-9-H-purine (**10**).* This compound was prepared as described for **9**. Obtained from compound **8** (0.35 g, 1.07 mmol) and triflate diisopropylphosphonomethanol (0.53 g, 1.61 mmol) as a yellowish amorphous solid (0.41 g, 76%). m.p. 56-58 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H, H-8), 5.51 (brs, 2H, NH_2), 4.86-4.81 [m, 2H, C*H*$(CH_3)_2$], 4.77-4.69 (m, 3H, H-1′ and H-2′ and H-3′), 4.15-4.13 (m, 1H, H-4′), 3.88-3.71 (m, 2H, PC*H*$_2$), 2.74-2.64 (m, 1H, H-5′), 2.34-2.29 (m, 1H, H-5′), 1.48 (s, 3H, C*H*$_3$), 1.32-1.27 (m, 15H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (C-2), 153.6 (C-4), 151.0 (C-6), 141.6 (C-8), 125.0 (C-5), 111.9 [*C*$(CH_3)_2$], 86.1 (d, $^{3}J_{P,C}$ = 10.9 Hz, C-4′), 84.7 (C-2′), 83.6 (C-3′), 71.2 [*C*H$(CH_3)_2$], 65.4 (d, $^{1}J_{P,C}$ = 169.4 Hz, P*C*H$_2$), 59.9 (C-1′), 34.9 (C-5′), 26.5 (CH_3), 24.1 (CH_3), 23.9 (CH_3), 23.8 (CH_3), 23.8 (CH_3) ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ 18.2 ppm. HRMS: $[M+H]^+$ calcd for $C_{20}H_{32}N_5O_6ClP$, 504.1773; found, 504.1774.

*5.1.5. 9-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]adenine (**11**).* A solution of compound **9** (0.50 g, 1.02 mmol) in methanolic ammonia (35 mL) was heated at 65 °C in a sealed bomb overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (20:1, DCM/MeOH) to afford compound **11** (0.34 g, 70% yield) as a white amorphous solid. m.p. 60-61 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (s, 1H, H-2), 8.16 (s, 1H, H-8), 6.19 (br, 2H, NH_2), 5.08-5.05 (m, 1H, H-1′), 4.91-4.89 (m, 1H, H-2′), 4.80-4.73 [m, 3H, H-3′ and C*H*$(CH_3)_2$], 4.17-4.14 (m, 1H, H-4′), 3.91-3.74 (m, 2H, PC*H*$_2$), 2.82-2.73 (m, 1H, H-5′), 2.39-2.33 (m, 1H, H-5′), 1.53 (s, 3H, CH_3), 1.36-1.28 (m, 15H, CH_3) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.2 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{29}N_5O_6P$, 430.1849; found, 430.1837.

*5.1.6. 9-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-dihydroxy-cyclopentan-1′-yl]adenine (**12**).* To the solution of compound **11** (0.30 g, 0.64 mmol) in MeOH (10 mL) was added PTSA (0.13 g, 0.70 mmol). The mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (10:1, DCM/MeOH) to afford compound **12** (0.24 g, 86% yield) as a white amorphous solid. m.p. 136-138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (s, 1H, H-2), 7.93 (s, 1H, H-8), 6.28 (br, 2H, NH_2), 4.81-4.68 [m, 3H, H-3′ and C*H*$(CH_3)_2$], 4.57-4.50 (m, 1H, H-1′), 4.27-4.25 (m, 1H, H-2′), 4.03-3.99 (m, 1H, H-4′), 3.84-3.80 (m, 2H, PC*H*$_2$), 2.92-2.84 (m, 1H, H-5′), 2.16-2.08 (m, 1H, H-5′), 1.31-1.27 (m, 12H, C*H*$_3$) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.9 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{29}N_5O_6P$, 430.1849; found, 430.1837.

*5.1.7. 9-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-dihydroxy-cyclopentan-1′-yl]-2-amino-6-chloro-9-H-purine (**13**).* Compound **13** was prepared as described for compound **12**. Obtained from compound **7** (0.31 g, 0.61 mmol) as a white amorphous solid (0.23 g, 80%). m.p. 95-96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (s, 1H, H-8), 5.97 (brs, 2H, NH_2), 5.62 (brs, 1H, OH), 4.77-4.69 [m, 5H, C*H*$(CH_3)_2$

and H-1′ and H-2′ and H-3′], 4.29 (brs, 1H, OH), 4.01-3.96 (m, 1H, H-4′), 3.89-3.74 (m, 2H, PCH_2), 2.78-2.71 (m, 1H, H-5′), 2.24-2.20 (m, 1H, H-5′), 1.33-1.30 (m, 12H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0 (C-2), 153.6 (C-4), 150.8 (C-6), 141.8 (C-8), 124.7 (C-5), 84.5 (d, $^3J_{P,C}$ = 12.6 Hz, C-4′), 75.6 (C-3′), 74.5 (C-2′), 71.7 [*C*H(CH_3)$_2$], 71.6 [*C*H(CH_3)$_2$], 65.4 (d, $^1J_{P,C}$ = 170.8 Hz, P*C*H_2), 59.2 (C-1′), 32.9 (C-5′), 26.5 (CH_3), 24.0 (CH_3), 23.9 (CH_3), 23.9 (CH_3) ppm.^{31}P NMR (121 MHz, $CDCl_3$): δ 19.8 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{28}N_5O_6ClP$, 464.1460; found, 464.1456.

*5.1.8. 9-[(1′S,3′S,4′S)-4′-Diisopropylphosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]adenine (**14**) and 9-[(1′R,2′R,4′S)-4′-Diisopropylphosphonomethoxy-2′-hydroxy-cyclopentan-1′-yl]adenine (**15**).* To a solution of compound **12** (0.34 g, 0.8 mmol) and DMAP (30 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (20 mL) was added 1,1′-thiocarbonyldiimidazole (0.28 g, 1.58 mmol) at room temperature. The mixture was stirred overnight. It was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To the residue in toluene (20 mL) was added azobis(isobutyronitrile) (0.052 mg, 0.316 mmol) and tributyltin hydride (0.85 mL, 3.16 mmol). The mixture was refluxed for 20 min. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (30:1, DCM/MeOH) to afford a mixture of compounds **14** and **15** (0.23 g, 70%) as a white foam. ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.5, 18.9 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{29}N_5O_5P$, 414.1900; found, 414.1898.

*5.1.9. 9-[(1′S,3′S,4′S)-4′-Diisopropylphosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]-2-amino-6-chloro-9-H-purine (**16**) and 9-[(1′R,2′R,4′S)-4′-Diisopropylphosphonomethoxy-2′-hydroxy-cyclopentan-1′-yl]-2-amino-6-chloro-9-H-purine (**17**).* The mixture of compounds **16** and **17** (70%) was prepared as described for compounds **14** and **15**. ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.9, 19.8 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{28}ClN_5O_5P$, 448.1510; found, 448.1510.

*5.1.10. 9-[(1′S,3′S,4′S)-4′-Phosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]adenine (**18**) and 9-[(1′R,2′R,4′S)-4′-Phosphonomethoxy-2′-hydroxy-cyclopentan-1′-yl]adenine (**19**).* To a solution of a mixture of compounds **14** and **15** (0.15 g, 0.36 mmol) in anhydrous CH_3CN (5 mL) was added bromotrimethylsilane (0.38 mL, 2.90 mmol) at 0 °C. The mixture was stirred at room temperature overnight and quenched with 1.0 M TEAB buffer (1 mL). The organic solvent was removed under reduced pressure and the water layer was lyophilized. The residue was first purified by silica gel column chromatography (10:1:0 to 10:5:1, DCM/MeOH/1.0 M TEAB) to give the crude product. Further purification using preparative reversed phase HPLC with a gradient of CH_3CN in 0.05 M TEAB solution (gradually ranging from 2% to 30% CH_3CN) gave compounds **18** (57 mg, 48% yield) and **19** (39 mg, 32% yield), both as a white amorphous solid.

*5.1.10.1. compound **18***: m.p. 150-153 °C. ^{1}H NMR (600 MHz, D_2O): δ 8.22 (s, 1H, H-8), 8.05 (s, 1H, H-2), 5.00-4.97 (m, 1H, H-1′), 4.46-4.44 (m, 1H, H-3′), 4.00-3.97 (m, 1H, H-4′), 3.68 (d, J = 9.4 Hz, 2H, PCH_2), 2.77-2.72 (m, 1H, H-5′), 2.32-2.28 (m, 2H, H-2′), 2.04-2.00 (m, 1H, H-5′) ppm. ^{13}C NMR (150 MHz, D_2O): δ 154.8 (C-6), 151.5 (C-2), 148.2 (C-4), 140.4 (C-8), 117.9 (C-5), 86.5 (d, $^{3}J_{P,C}$ = 11.9 Hz, C-4′), 74.2 (C-3′), 66.0 (d, $^{1}J_{P,C}$ = 156.8 Hz, PCH$_2$), 51.4 (C-1′), 38.0 (C-2′), 35.7 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 14.3 ppm. HRMS: [M-H]$^-$ calcd for $C_{11}H_{15}N_5O_5P$, 328.0816; found, 328.0812.

*5.1.10.2. compound **19***: m.p. 170-172 °C. ^{1}H NMR (600 MHz, D_2O): δ 8.35 (s, 1H, H-8), 8.15 (s, 1H, H-2), 4.72-4.70 (m, 1H, H-2′), 4.67-4.65 (m, 1H, H-1′), 4.27-4.23 (m, 1H, H-4′), 3.46-3.44 (m, 2H, PCH_2), 2.80-2.77 (m, 1H, H-3′), 2.37-2.33 (m, 1H, H-5′), 2.17-2.13 (m, 1H, H-3′), 1.98-1.93 (m, 1H, H-5′) ppm. ^{13}C NMR (150 MHz, D_2O): δ 155.1 (C-6), 151.9 (C-2), 148.9 (C-4), 140.8 (C-8), 118.2 (C-5), 77.1 (d, $^{3}J_{P,C}$ = 11.7 Hz, C-4′), 74.8 (C-2′), 66.9 (d, $^{1}J_{P,C}$ = 151.6 Hz, PCH$_2$), 58.6 (C-1′), 37.2 (C-3′), 35.7 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 15.9 ppm. HRMS: [M-H]$^-$ calcd for $C_{11}H_{15}N_5O_5P$, 328.0816; found, 328.0813.

*5.1.11. 9-[(1'S,3'S,4'S)-4'-Phosphonomethoxy-3'-hydroxy-cyclopentan-1'-yl]-2-amino-6-chloro-9-H-purine (**20**) and 9-[(1'R,2'R,4'S)-4'-Phosphonomethoxy-2'-hydroxy-cyclopentan-1'-yl]-2-amino-6-chloro-9-H-purine (**21**).* The mixture of compounds **20** and **21** (71%) was prepared as described for **18** and **19**, butwithout separation for next step. HRMS: [M-H]$^-$ calcd for $C_{11}H_{14}N_5O_5P$, 362.0426; found, 362.0429.

*5.1.12. 9-[(1'S,3'S,4'S)-4'-Phosphonomethoxy-3'-hydroxy-cyclopentan-1'-yl]guanine (**22**) and 9-[(1'R,2'R,4'S)-4'-Phosphonomethoxy-2'-hydroxy-cyclopentan-1'-yl]guanine (**23**).* To a solution of the mixture of **20** and **21** (0.20 g, 0.54 mmol) in dioxane (20 mL) was added 4N NaOH (10 mL). The mixture was refluxed for 4 h. It was neutralized by adding 4N HCl after cooling to room temperature. The organic solvent was removed under reduced pressure and the water layer was lyophilized. The first purification by silica gel flash chromatography and further purification by RP-HPLC followed the same method as described for compounds **18** and **19**. It furnished the pure compounds **22** (90 mg, 48%) and **23** (54 mg, 29%), both as a white amorphous solid.

*5.1.12.1. compound **22***: m.p. 185-187 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.73 (s, 1H, H-8), 4.51-4.45 (m, 1H, H-1′), 4.01-3.95 (m, 1H, H-3′), 3.81-3.75 (m, 1H, H-4′), 3.46-3.43 (m, 2H, PCH_2), 2.55-2.46 (m, 1H, H-5′), 2.05-2.00 (m, 2H, H-2′), 1.72-1.64(m, 1H, H-5′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 158.8 (C-6), 153.7 (C-2), 150.9 (C-4), 137.7 (C-8), 115.6 (C-5), 86.5 (d, $^{3}J_{P,C}$ = 10.5 Hz, C-4′), 74.1 (C-3′), 66.4 (d, $^{1}J_{P,C}$ = 151.1 Hz, PCH$_2$), 50.8 (C-1′), 37.6 (C-2′), 35.9 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 13.2 ppm. HRMS: [M-H]$^-$ calcd for $C_{11}H_{15}N_5O_6P$, 344.0765; found, 344.0765.

*5.1.12.2. compound **23***: m.p. 220-222 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.81 (s, 1H, H-8), 4.53-4.49 (m,

1H, H-2′), 4.34-4.29 (m, 1H, H-1′), 4.15-4.14 (m, 1H, H-4′), 3.49-3.46 (m, 2H, PCH_2), 2.66-2.60 (m, 1H, H-5′), 2.25-2.20 (m, 1H, H-3′), 1.98-1.93(m, 1H, H-5′), 1.87-1.81 (m, 1H, H-3′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 158.4 (C-6), 153.3 (C-2), 151.4 (C-4), 138.0 (C-8), 115.6 (C-5), 77.6 (d, $^3J_{P,C}$ = 13.4 Hz, C-4′)), 74.6 (C-2′), 66.4 (d, $^1J_{P,C}$ = 153.5 Hz, P*C*H_2), 60.3 (C-1′), 37.2 (C-3′), 35.6 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 13.6 ppm. HRMS: $[M-H]^-$ calcd for $C_{11}H_{15}N_5O_6P$, 344.0765; found, 344.0768.

*5.1.13. 1-[(1′R,2′S,3′R,4′S)-4′-Hydroxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]thymine (**25**).* To a solution of compound **4** (0.40 g, 2.31 mmol) in dioxane (30 mL) was added ethyl [(2*E*)-3-ethoxy-2-methylprop-2-enoyl] carbamate **24** (0.46 g, 2.31 mmol). The mixture was heated at 100 °C for 3 h. The solvent was removed under reduced pressure, and the residue was used for cyclization without further purification. Aq. ammonia (20 mL) was added to the residue in a sealed bomb at 90 °C overnight. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (30:1, DCM/MeOH) to afford compound **25** (0.56 g, 85%) as a white amorphous solid. m.p. 88-90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.0 (brs, 1H, NH), 7.31 (d, J = 1.1 Hz, 1H, H-6), 4.90 (dd, J = 2.1, 5.9 Hz, 1H, H-2′), 4.65 (d, J = 5.9 Hz, 1H, H-1′), 4.56 (m, 1H, H-3′), 4.33 (s, 1H, H-4′), 2.76-2.66 (m, 1H, H-5′), 2.05-2.00 (m, 1H, H-5′), 1.89 (s, 3H, T C*H*$_3$), 1.48 (s, 3H, C*H*$_3$), 1.30 (s, 3H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.3 (C-4), 151.2 (C-2), 140.3 (C-6), 111.6 [*C*$(CH_3)_2$], 110.8 (C-5), 87.2 (C-3′), 84.3 (C-2′), 76.1 (C-4′), 66.1 (C-1′), 37.8 (C-5′), 26.7 (CH_3), 24.3 (CH_3), 12.2 (T *C*H_3) ppm. HRMS: $[M+H]^+$ calcd for $C_{13}H_{19}N_2O_5$, 283.1288; found, 283.1288.

*5.1.14. 1-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]thymine (**26**).* Compound **26** was prepared as described for compound **9**. Obtained from compound **25** (0.60 g, 2.13 mmol) and tosylate diisopropylphosphonomethanol (1.49 g, 4.25 mmol) as a yellowish amorphous solid (0.82 g, 84%). m.p. 45-47 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (brs, 1H, NH), 7.31 (s, 1H, H-6), 4.88-4.83 (m, 1H, H-2′), 4.79-4.71 (m, 3H, H-3′ and C*H*$(CH_3)_2$), 4.67-4.65 (m, 1H, H-4′), 4.05-4.01 (m, 1H, H-1′), 3.91-3.73 (m, 2H, PC*H*$_2$), 2.67-2.57 (m, 1H, H-5′), 2.13-2.05 (m, 1H, H-5′),1.95 (s, 3H, T C*H*$_3$), 1.49 (s, 3H, C*H*$_3$), 1.34-1.29 (m, 15H, C*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (C-4), 150.9 (C-2), 138.2 (C-6), 112.2 [*C*$(CH_3)_2$], 110.8 (C-5), 85.8 (d, $^3J_{P,C}$ = 12.8 Hz, C-4′), 83.9 (C-3′), 83.6 (C-2′), 71.2 [*C*H$(CH_3)_2$], 71.1 [*C*H$(CH_3)_2$], 65.5 (d, $^1J_{P,C}$ = 169.0 Hz, P*C*H_2), 61.8 (C-1′), 34.9 (C-5′), 26.6 (CH_3), 24.3(CH_3), 23.9 (CH_3), 23.9(CH_3), 12.3 (T *C*H_3) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 18.9 ppm. HRMS: $[M+H]^+$ calcd for $C_{20}H_{34}N_2O_8P$, 461.2047; found, 461.2047.

*5.1.15. 1-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-dihydroxy-cyclopentan-1′-yl]thymine (**27**).* Compound **27** was prepared as described for compound **12**. Obtained from compound **27** (0.4 g, 1.18 mmol) as a white amorphous solid (0.3 g, 85%). m.p. 64-67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.4 (brs, 1H, NH), 7.31 (s, 1H, H-6), 5.07-4.71 [m, 5H, C*H*$(CH_3)_2$ and H-1′ and H-2′ and H-3′], 4.28 (brs, 1H,

OH), 4.17 (brs, 1H, OH), 3.92-3.75 (m, 3H, H-4′ and PCH_2), 2.75-2.64 (m, 1H, H-5′), 1.89 (s, 3H, T CH_3), 1.68-1.61 (m, 1H, H-5′), 1.49 (s, 3H, CH_3), 1.34-1.31 (m, 12H, CH_3) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.8 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{30}N_2O_8P$, 421.1734; found, 421.1735.

5.1.16. 1-[(1'S,3'S,4'S)-4'-Diisopropylphosphonomethoxy-3'-hydroxy-cyclopentan-1'-yl]thymine ***(28)*** *and 1-[(1'R,2'R,4'S)-4'-Diisopropylphosphonomethoxy-2'-hydroxy-cyclopentan-1'-yl]thymine* ***(29)***. The mixture of compounds **28** and **29** was prepared as described for compounds **14** and **15**. Obtained from compound **27** (0.40 g, 1.18 mmol) as a white foam (0.34 g, 85%). ^{31}P NMR (121 MHz, $CDCl_3$): δ 19.8, 19.6 ppm. HRMS: $[M+H]^+$ calcd for $C_{17}H_{30}N_2O_7P$, 405.1785; found, 405.1783.

5.1.17. 1-[(1'S,3'S,4'S)-4'-Phosphonomethoxy-3'-hydroxy-cyclopentan-1'-yl]thymine ***(30)*** *and 1-[(1'R,2'R,4'S)-4'-Phosphonomethoxy-2'-hydroxy-cyclopentan-1'-yl]thymine* ***(31)***. Compounds **30** and **31** were prepared as described for compounds **18** and **19**. Obtained from compounds **28** and **29** (0.25 g, 0.61 mmol) as a white amorphous solid (0.17 g, 85%).

5.1.17.1. compound ***30***: m.p. 180-182 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.63 (s, 1H, H-6), 5.04-5.00 (m, 1H, H-1′), 4.37-4.34 (m, 1H, H-3′), 3.87-3.84 (m, 1H, H-4′), 3.58-3.46 (m, 2H, PCH_2), 2.57-2.51 (m, 1H, H-5′), 2.14-2.08 (m, 1H, H-2′), 2.06-2.01 (m, 1H, H-2′), 1.87 (s, 3H, T CH_3), 1.80-1.74 (m, 1H, H-5′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 168.6 (C-4), 152.4 (C-2), 139.9 (C-6), 111.3 (C-5), 86.2 (d, $^3J_{P,C}$ = 10.2 Hz, C-4′), 74.2 (C-3′), 68.3 (d, $^1J_{P,C}$ = 151.2 Hz, PCH_2), 52.4 (C-1′), 36.1 (C-2′), 34.4 (C-5′), 11.4 (T CH_3) ppm. ^{31}P NMR (121 MHz, D_2O): δ 13.4 ppm. HRMS: $[M-H]^-$ calcd for $C_{11}H_{16}N_2O_7P$, 319.0700; found, 319.0697.

5.1.17.2. compound ***31***: m.p. 170-172 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.64 (s, 1H, H-6), 5.04-5.00 (1H overlap, H-1′), 4.49-4.44 (m, 1H, H-2′), 4.13 (brs, 1H, H-4′), 3.42 (d, J = 9.4 Hz, 2H, PCH_2), 2.58-2.52 (m, 1H, H-5′), 2.28-2.24 (m, 1H, H-3′), 1.87 (s, 3H, T CH_3), 1.86-1.76 (m, 2H, H-3′ and H-5′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 167.9 (C-4), 153.9 (C-2), 139.2 (C-6), 111.5 (C-5), 76.8 (d, $^3J_{P,C}$ = 11.5 Hz, C-4′), 73.5 (C-3′), 67.0 (d, $^1J_{P,C}$ = 151.1 Hz, PCH_2), 61.1 (C-1′), 37.1 (C-3′), 34.5 (C-5′), 11.5 (T CH_3) ppm. ^{31}P NMR (121 MHz, D_2O): δ 13.5 ppm. HRMS: $[M-H]^-$ calcd for $C_{11}H_{16}N_2O_7P$, 319.0700; found, 319.0702.

5.1.18. 1-[(1'R,2'S,3'R,4'S)-4'-Hydroxy-2',3'-O-isopropylidene-cyclopentan-1'-yl]uracil ***(33)***. To a solution of 3-ethoxyacrylic acid (2.0 g, 17.22 mmol) in DCM (70 mL) was added thionyl chloride (1.89 mL, 25.8 mmol) at 0 °C. The mixture was refluxed for 3 h and then concentrated to get the residue (*E*)-3-ethoxyacryloyl chloride for next step. To a solution of the residue in toluene (10 mL) was added silver cynate (3.89 g, 25.98 mmol). The mixture was refluxed for 30 min and cooled to room temperature. The supernatant liquor was added to a solution of compound **4** (1.5 g, 8.66 mmol) in DMF (15 mL) at −15 °C. The reaction was stirred at −15 °C for 2 h and then stirred at room temperature overnight. The solvent

was removed under reduced pressure and the residue was used for cyclization without further purification. Aq. ammonia (20 mL) was added to the residue in a sealed bomb at 90 °C overnight. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20:1, DCM/MeOH) to afford compound **33** (2.2 g, 80%) as a white amorphous solid. m.p. 185-187 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.26 (brs, 1H, NH), 7.81 (d, J = 8.0 Hz, 1H, H-6), 5.58 (d, J = 8.0 Hz, 1H, H-5), 5.46 (d, J = 3.1 Hz, 1H, OH), 4.73-4.72 (m, 1H, H-2′), 4.68-4.65 (m, 1H, H-1′), 4.43 (dd, J = 2.1, 6.5 Hz, 1H, H-3′), 4.04 (s, 1H, H-4′), 2.36-2.32 (m, 1H, H-5′), 1.87-1.83 (m, 1H, H-5′), 1.39 (s, 3H, CH_3), 1.21 (s, 3H, CH_3) ppm. ^{13}C NMR (150 MHz, DMSO-d_6): δ 163.3 (C-4), 151.1 (C-2), 143.6 (C-6), 111.1 [C(CH$_3$)$_2$], 101.1 (C-5), 86.2 (C-3′), 83.4 (C-2′), 74.5 (C-4′), 61.2 (C-1′), 36.9 (C-5′), 26.8 (CH$_3$), 24.6 (CH$_3$) ppm. HRMS: [M+H]$^+$ calcd for $C_{12}H_{17}N_2O_5$, 269.1131; found, 269.1125.

*5.1.19. 1-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-O-isopropylidene-cyclopentan-1′-yl]uracil (**34**).* Compound **34** was prepared as described for compound **9**. Obtained from compound **33** (0.40 g, 1.49 mmol) and tosylate diisopropylphosphonomethanol (1.0 g, 2.98 mmol) as a yellowish amorphous solid (0.61 g, 92%). m.p. 56-58 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 9.63 (brs, 1H, NH), 7.56 (d, J = 8.1 Hz, 1H, H-6), 5.72 (dd, J = 2.3, 8.1 Hz, 1H, H-5), 4.94-4.89 (m, 1H, H-2′), 4.80-4.66 (m, 4H, H-3′ and H-1′ and CH(CH$_3$)$_2$), 4.06-4.03 (m, 1H, H-4′), 3.87-3.72 (m, 2H, PCH_2), 2.69-2.59 (m, 1H, H-5′), 2.09-2.03 (m, 1H, H-5′), 1.49 (s, 3H, CH_3), 1.35-1.30 (m, 12H, CH_3) ppm. ^{31}P NMR (121 MHz, CDCl$_3$): δ 18.9 ppm. HRMS: [M+H]$^+$ calcd for $C_{17}H_{32}N_2O_8P$, 446.18178; found, 447.1886.

*5.1.20. 1-[(1′R,2′S,3′R,4′S)-4′-Diisopropylphosphonomethoxy-2′,3′-dihydroxy-cyclopentan-1′-yl]uracil (**35**).* Compound **35** was prepared as described for compound **12**. Obtained from compound **34** (0.5 g, 1.12 mmol) as a white foam (0.39 g, 85%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.50 (d, J = 8.1 Hz, 1H, H-6), 5.72 (d, J = 8.1 Hz, 1H, H-5), 4.93-4.85 (m, 1H, H-1′), 4.80-4.70 (m, 2H, CH(CH$_3$)$_2$), 4.29-4.25 (m, 1H, H-3′), 4.19-4.17 (m, 1H, H-4′), 3.95-3.91 (m, 1H, H-2′), 7.56 (d, J = 9.1 Hz, 2H, PCH$_2$), 2.73-2.64 (m, 1H, H-5′), 1.74-1.70 (m, 1H, H-5′), 1.35-1.31 (m, 12H, CH$_3$) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ 163.6 (C-4), 152.0 (C-2), 142.4 (C-6), 103.4 (C-5), 84.5 (d, $^{3}J_{P,C}$ = 10.2 Hz, C-4′), 74.4 (C-3′), 72.0 [CH(CH$_3$)$_2$], 71.9 (C-2′), 71.8 [CH(CH$_3$)$_2$], 66.1 (d, $^{1}J_{P,C}$ = 164.8 Hz, PCH$_2$), 60.5 (C-1′), 33.4 (C-5′), 24.3 (CH$_3$) ppm. ^{31}P NMR (121 MHz, CDCl$_3$): δ 19.8 ppm. HRMS: [M+H]$^+$ calcd for $C_{16}H_{28}N_2O_8P$, 407.1577; found, 407.1569.

*5.1.21. 1-[(1′R,3′R,4′S)-4′-Diisopropylphosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]uracil (**36**) and 1-[(1′R,2′S,4′S)-4′-diisopropylphosphonomethoxy-2′-hydroxy-cyclopentan-1′-yl]uracil (**37**).* Compounds **36** and **37** were prepared as described for compounds **14** and **15**. Obtained from compound **35** (0.1 g, 0.24 mmol) as a white foam (75 mg, 79%). HRMS: [M+H]$^+$ calcd for $C_{16}H_{28}N_2O_7P$, 491.1628; found, 391.1628.

*5.1.22. 1-[(1′R,3′R,4′S)-4′-Diisopropylphosphonomethoxy-3′-O-tert-butyldimethylsily-cyclopentan-1′-yl]uracil (**38**) and 1-[(1′R,2′S,4′S)-4′-Diisopropylphosphonomethoxy-3′-O-tert-butyldimethylsily-cyclopentan-1′-yl]uracil (**39**).* To a mixture of compounds **36** and **37** (0.30 g, 0.76 mmol) in DMF (10 mL) was added imidazole (0.15 g, 2.31 mmol) and *tert*-butyldimethylchlorosilane (0.24 g, 1.61 mmol). The reaction mixture was stirred at room temperature overnight. It was partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (30:1, DCM/MeOH) to afford a mixture of compounds **38** and **39** (0.31 g, 80%) as a white solid. HRMS: $[M-H]^-$ calcd for $C_{22}H_{42}N_2O_7PSi$, 505.2493; found, 505.2492.

*5.1.23. 1-[(1′S,3′S,4′S)-4′-Phosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]cytosine (**40**) and 1-[(1′R,2′R,4′S)-4′-Phosphonomethoxy-2′-hydroxy -cyclopentan-1′-yl]cytosine (**41**).* To a solution of a mixture of compounds **38** and **39** (0.25 g, 0.49 mmol) in CH_3CN (15 mL) was added 2,4,6-triisopropylbenzenesulfonyl chloride (0.375 g, 1.24 mmol) and Et_3N (0.34 mL, 2.48 mmol). The mixture was stirred at room temperature overnight. Aq. ammonia was added to the above solution when compound **38** and **39** disappeared according to TLC analysis. The mixture was stirred for 0.5 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (20:1, DCM/MeOH). The product was used for the next step. To a solution of the product (0.20 g, 0.39 mmol) in THF (7 mL) was added triethylamine trihydrofluoride (0.13 mL, 0.79 mmol). The mixture was stirred at room temperature overnight. TMSOMe (0.2 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was partitioned between H_2O and EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (10:1, DCM/MeOH) to afford a mixture of compounds **40** and **41** (0.125 g, 80%) as a white solid. HRMS: $[M+H]^+$ calcd for $C_{16}H_{29}N_3O_6P$, 390.1788; found, 390.1782.

*5.1.24. 1-[(1′S,3′S,4′S)-4′-Phosphonomethoxy-3′-hydroxy-cyclopentan-1′-yl]cytosine (**42**) and 1-[(1′R,2′R,4′S)-4′-Phosphonomethoxy-2′-hydroxy-cyclopentan-1′-yl]cytosine (**43**).* Compounds **42** and **43** were prepared as described for compounds **18** and **19**. Obtained from compounds **40** and **41** (0.10 g, 0.25 mmol) as a white amorphous solid (63 mg, 79%).

*5.1.24.1. compound **42***: m.p. 158-160 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.89-7.88 (d, J = 7.56 Hz, 1H, H-6), 6.09-6.07 (d, J = 7.53 Hz, 1H, H-5), 5.20-5.17 (m, 1H, H-1′), 4.42-4.41 (m, 1H, H-3′), 3.93-3.91 (m, 1H, H-4′), 3.71-3.68 (m, 2H, PCH_2), 2.63-2.58 (m, 1H, H-5′), 2.20-2.16 (m, 1H, H-2′), 2.09-2.04 (m, 1H, H-2′), 1.84-1.80 (m, 1H, H-5′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 164.7 (C-4), 157.2 (C-2), 144.4 (C-6), 96.3 (C-5), 86.4 (d, $^3J_{P,C}$ = 12.1 Hz, C-4′), 74.4 (C-3′), 65.9 (d, $^1J_{P,C}$ = 156.8 Hz, P*C*H_2), 53.9 (C-1′), 37.4 (C-2′), 34.8 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 15.5 ppm. HRMS: $[M-H]^-$ calcd for $C_{10}H_{15}N_3O_6P$, 304.0703; found, 304.0708.

*5.1.24.2. compound **43***: m.p. 167-169 °C. ^{1}H NMR (500 MHz, D_2O): δ 7.89-7.88 (d, J = 7.45 Hz, 1H, H-6), 6.11-6.10 (d, J = 7.47 Hz, 1H, H-5), 5.04-5.00 (1H overlap, H-1′), 4.51-4.47 (m, 1H, H-2′), 4.15-4.13 (m, 1H, H-4′), 3.44-3.43 (d, J = 9.50 Hz, 2H, PCH_2), 2.63-2.58 (m, 1H, H-5′), 2.31-2.27 (m, 1H, H-3′),1.88-1.84 (m, 1H, H-3′) 1.82-1.79(m, 1H, H-5′) ppm. ^{13}C NMR (125 MHz, D_2O): δ 165.6 (C-4), 158.7 (C-2), 143.8 (C-6), 99.5(C-5), 77.7 (d, $^{3}J_{P,C}$ = 11.9 Hz, C-4′), 74.8 (C-2′), 66.8 (d, $^{1}J_{P,C}$ = 151.3 Hz, PCH_2), 62.0 (C-1′), 37.5 (C-3′), 35.2 (C-5′) ppm. ^{31}P NMR (121 MHz, D_2O): δ 13.5 ppm.HRMS: $[M-H]^-$ calcd for $C_{10}H_{15}N_3O_6P$, 304.0703; found, 304.0695.

*5.1.25. 9-[(1'S,3'S,4'S)-4'-O-(N,N'-Bis(isopropyl-L-alaninate)methylphosphonodiamidate)-3'-hydroxy-cyclopentan-1'-yl]guanine (**44**).* To a solution of compound **42** (30 mg, 0.067 mmol) and L-alanine isopropyl ester HCl (68 mg, 0.4 mmol) in anhydrous pyridine (4 mL) was added Et_3N (0.065 mL, 0.47 mmol). The mixture was stirred at 60 °C under nitrogen for 20 min. Another solution of 2,2′-dithiodipyridine (103 mg, 0.47 mmol) and PPh_3 (123 mg, 0.47 mmol) in anhydrous pyridine (1 mL) was made and stirred for 15 min to give a clear light yellow solution. This solution was added to the above solution, and the combined reaction mixture was stirred at 60 °C for 12 h. The solvent was removed under reduced pressure and the residue was partitioned between H_2O and EtOAc. The organic layer was washed with sat. $NaHCO_3$ and brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (10:1, DCM/MeOH). Further purification using preparative reversed phase HPLC with a gradient of CH_3CN in water (ranging from 40% to 90% CH_3CN) gave compound **44** (14 mg, 36%) as a white amorphous solid. m.p. 90-92 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.75 (s, 1H, H-8), 6.47 (brs, 2H, NH_2), 5.09 (s, 1H, OH), 4.91-4.84 (m, 3H, CH(CH_3)$_2$ and H-1′), 4.58-4.54 (m, 1H, NH), 4.45-4.42 (m, 1H, NH), 4.18 (s, 1H, H-3′), 3.87-3.79 (m, 2H, Ala-CH), 3.78-3.77 (m, 1H, H-4′), 3.67-3.65 (m, 2H, PCH_2), 2.50 (1H overlap H-5′), 2.13-2.09 (m, 1H, H-2′), 2.05-2.01 (m, 1H, H-2′), 1.88-1.84 (m, 1H, H-5′), 1.27 (dd, J = 2.4, 7.1 Hz, 6H, Ala-CH_3), 1.20-1.16 (m, 12H, CH(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.62, 173.60 (Ala-CO), 157.1 (C-6), 153.6 (C-2), 151.1 (C-4), 135.6 (C-8), 116.6 (C-5), 87.0 ($^{3}J_{P,C}$ = 11.7 Hz, C-4′), 73.6 (C-3′), 67.8 (C-1′), 66.0 ($^{1}J_{P,C}$ = 135.3 Hz, PCH_2), 50.7 [CH(CH_3)$_2$], 48.3 (Ala-CH), 40.1 (C-2′), 36.6 (C-5′), 21.5 [CH(CH$_3$)$_2$], 20.8 (Ala-CH_3) ppm. ^{31}P NMR (121 MHz, D_2O): δ 20.6 ppm. HRMS: $[M+H]^+$ calcd for $C_{23}H_{39}N_7O_8P$, 572.2592; found, 572.2609.

*5.1.26. 9-[(1'R,2'R,4'S)-4'-O-(N,N'-Bis(isopropyl-L-alaninate)methylphosphonodiamidate)-2'-hydroxy-cyclopentan-1'-yl]guanine (**45**).* Compound **45** was prepared as described for compound **44**. Obtained from compound **43** (24 mg, 0.053 mmol) as a white amorphous solid (10 mg, 33%). m.p. 115-118 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.74 (s, 1H, H-8), 6.42 (brs, 2H, NH_2), 5.26 (s, 1H, OH), 4.92-4.86 (m, 2H, CH(CH_3)$_2$), 4.58-4.54 (m, 1H, NH), 4.50-4.44 (m, 1H, H-2′), 4.43-4.40 (m, 1H, NH), 4.34-4.30(m, 1H, H-1′), 4.07-4.05 (m, 1H, H-4′), 3.87-3.80 (m, 2H, Ala-CH),3.67-3.65 (d, J = 8.5 Hz, 2H, PCH_2), 2.50

(1H overlap H-5′), 2.09-2.05 (m, 1H, H-3′), 1.99-1.95 (m, 1H, H-5′), 1.79-1.75 (m, 1H, H-3′), 1.28 (dd, *J* = 1.7, 7.1 Hz, 6H, Ala-CH_3), 1.21-1.18 (m, 12H, CH(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.63, 173.60 (Ala-CO), 156.9 (C-6), 153.3 (C-2), 151.4 (C-4), 136.1 (C-8), 116.8 (C-5), 77.8 ($^3J_{P,C}$ = 12.8 Hz, C-4′), 73.9 (C-2′), 67.8 [*C*H(CH$_3$)$_2$], 66.0 ($^1J_{P,C}$ = 135.1 Hz, PCH$_2$), 60.1 (C-1′), 48.3 (Ala-CH), 38.8 (C-3′), 36.1 (C-5′), 21.5 [CH(*C*H$_3$)$_2$], 20.7 (Ala-CH$_3$) ppm. ^{31}P NMR (121 MHz, D$_2$O): δ 20.6 ppm. HRMS: [M-H]$^-$ calcd for $C_{23}H_{37}N_7O_8P$, 570.2446; found, 570.2448.

5.2. Antiviral evaluation

The compounds were evaluated against the following viruses: herpes simplex virus 1 (HSV-1) strain KOS, thymidine kinase-deficient (TK−) HSV-1 KOS strain resistant to ACV (ACVr), herpes simplex virus 2 (HSV-2) strains Lyons and G, varicella-zoster virus (VZV) strain Oka, TK− VZV strain 07−1, human cytomegalovirus (HCMV) strains AD-169 and Davis. The antiviral assays are based on inhibition of virus-induced cytopathicity (HSV and HCMV) or plaque formation (VZV) in human embryonic lung (HEL) fibroblasts. Confluent cell cultures in microtiter 96-well plates are inoculated with 100 CCID50 of virus (1 CCID50 being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) (VZV). After 2 hours of adsorption, the viral inoculum is removed and the cultures are further incubated in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation is recorded after 2-3 (HSV), 5 (VZV) or 6-7 (HCMV) days post-infection. Antiviral activity is expressed as the EC_{50} or compound concentration required inhibiting virus-induced cytopathicity or viral plaque formation by 50%.

The cytostatic activity measurements are based on the inhibition of cell growth. HEL cells are seeded at a rate of 5 x 10^3 cells/well into 96-well microtiter plates and allow proliferating for 24 hours. Then, medium containing different concentrations of the test compounds is added. After 3 days of incubation at 37 °C, the cell number is determined with a Coulter counter. The cytostatic concentration is calculated as the CC_{50}, or the compound concentration required reducing cell proliferation by 50% relative to the number of cells in the untreated controls. CC_{50} values are estimated from graphic plots of the number of cells (percentage of control) as a function of the concentration of the test compounds. Alternatively, cytotoxicity of the test compounds is expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that causes a microscopically detectable alteration of cell morphology.

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Notes

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data related to this article was uploaded.

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Highlights

- The synthesis of eight cyclopentyl nucleoside phosphonates was carried out.
- The 3′-deoxy guanosine analogue displayed promising activity against VZV.
- The 3′-deoxy guanosine analogue lacked cytotoxicity.
- The corresponding phosphonodiamidate prodrugs was devoid of antiviral activity.

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