Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Tetrahedron 89 (2021) 132159

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of phosphonate derivatives of 2′-deoxy-2′-fluorotetradialdose D-nucleosides and tetradialdose D-nucleosides

Tomáš Lášek [a, b], Juraj Dobiáš [a], Miloš Buděšínský [a], Jaroslav Kozák [a], Barbora Lapuníková [a], Ivan Rosenberg [a], Gabriel Birkuš [a], Ondřej Páv [a, *]

[a] IOCB Prague, Flemingovo Nám. 2, 160 00, Prague, Czech Republic
[b] UCT Prague, Technická 5, 166 28, Prague, Czech Republic

ARTICLE INFO

Article history:
Received 4 March 2021
Received in revised form
2 April 2021
Accepted 9 April 2021
Available online 16 April 2021

Keywords:
Nucleoside phosphonate
Triphosphate
Prodrug
Tetradialdose D-nucleoside
2′-Fluoronucleoside

ABSTRACT

Analogs of nucleosides and nucleotides represent a promising pool of potential therapeutics. This work describes a new synthetic route leading to 2′-deoxy-2′-fluorotetradialdose D-nucleoside phosphonates. Moreover, a new universal synthetic route leading to tetradialdose D-nucleosides bearing purine nucleobases is also described. All new compounds were tested as triphosphate analogs for inhibitory potency against a variety of viral polymerases. The fluorinated nucleosides were transformed to phosphoramidate prodrugs and evaluated in cell cultures against various viruses including influenza and SARS-CoV-2.

1. Introduction

Synthesis of phosphonate derivatives of nucleosides, followed by the preparation of an appropriate phosphonodiphosphate or a prodrug form, represents a validated approach in the search for novel nucleoside-based antiviral agents [1]. In general, the introduction of a phosphonate group brings several advantages. It directly bypasses the first phosphorylation step in the cascade, which is often the rate-limiting step, leading to a biologically active nucleoside triphosphate. Moreover, unlike nucleoside monophosphates, phosphonates exhibit increased metabolic stability against cleavage by phosphoesterases [1]. To profile their biological activity, the phosphonodiphosphates and lipophilic prodrugs of phosphonate derivatives of nucleosides were prepared. The former can be used directly in enzyme assays, whereas the latter can be screened in cell-based assays due to the improved uptake compared to parent nucleotides.

Continuing our search for novel nucleoside phosphonates [2–4], we turned our attention to a tetradialdose nucleosides bearing *O*-phosphonomethyl group. Tetradialdose nucleoside **1** was first prepared by Kim et al., in 1991 (Fig. 1) [5]. More recently, teams of Herdewijn [6,7] (**2**, **3**) and Cihlář [8] (**4**) reported synthesis of 3′-fluoro nucleosides and nucleosides derived from L-sugars. Potent anti-HIV activity was reported in the case of compound **4**. The potential of 2′-fluoro nucleosides has been demonstrated by the use of sofosbuvir, an approved medication used to treat HCV [9]. Surprisingly, the synthesis of D-2′-fluorotetradialdose nucleoside phosphonates has not been reported so far. Moreover, in the case of D-tetraaldose phosphonates bearing purine nucleobase, only the synthesis of adenine derivative **1** has been published [5]. Therefore, we report here the synthesis of novel 2′-fluorotetradialdose nucleoside phosphonates **5** and phosphonate analogs **6** (Fig. 2), and their biochemical evaluation against several types of viruses including influenza and coronavirus.

2. Results and discussion

2.1. Synthesis of D-2′-fluorotetradialdose nucleoside phosphonates

The synthetic strategy leading to 2′-fluoro analogs was developed based on the previously published synthetic route leading to L-dialdose analogs **3** [7]. Starting from L-xylose **7,** we prepared methyl glycoside **9** with 5′-protected hydroxyl in two steps (Scheme 1). The first key step of the synthetic sequence consisted of

* Corresponding author.
E-mail address: ondrej.pav@uochb.cas.cz (O. Páv).

https://doi.org/10.1016/j.tet.2021.132159
0040-4020/

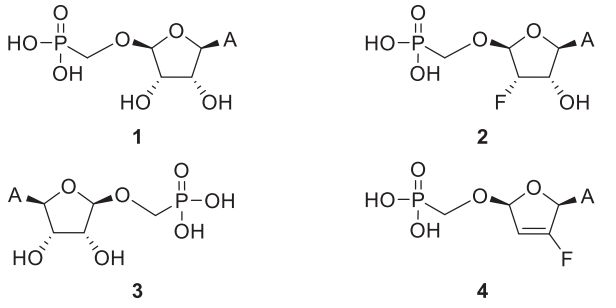
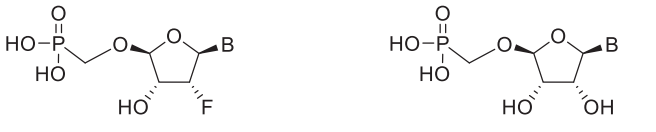


Fig. 1. Examples of the reported tetradialdose nucleoside phosphonates.

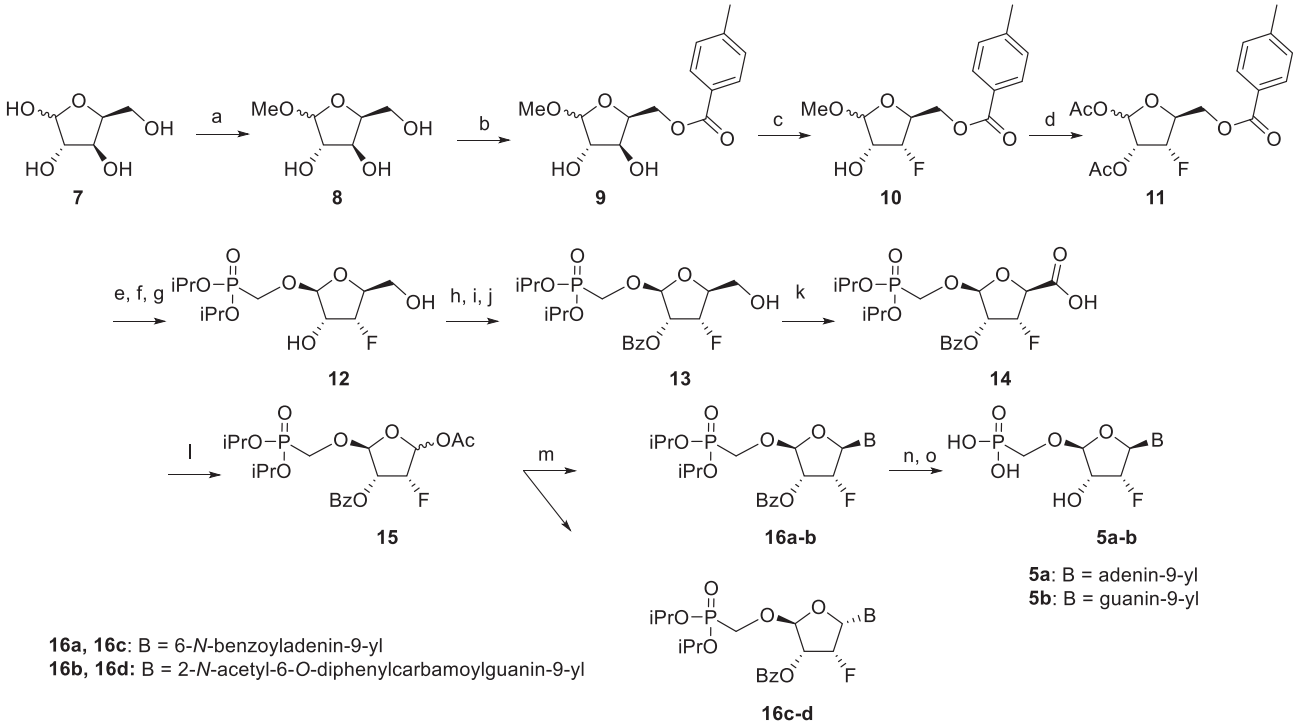


5a: B = adenin-9-yl
5b: B = guanin-9-yl

1: B = adenin-9-yl
6a: B = guanin-9-yl
6b: B = 8-azaadenin-9-yl
6c: B = 8-azaguanin-9-yl

Fig. 2. Structures of the prepared tetradialdose nucleoside phosphonates.

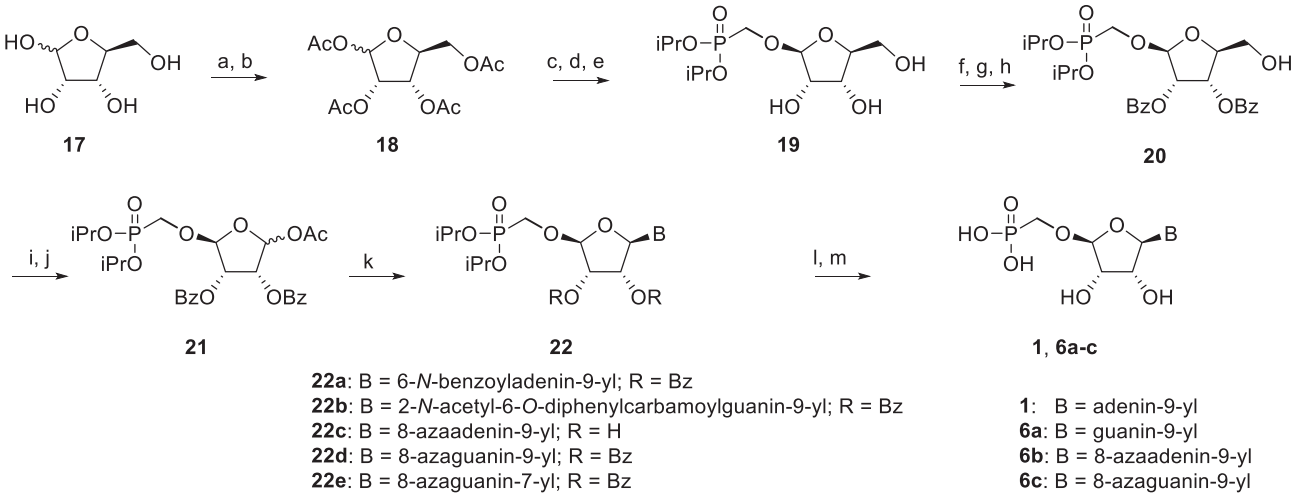
the introduction of the fluorine atom. To avoid elimination reactions and the formation of side products during the fluorination step, it was reported that the reaction had to be performed on a precursor bearing unprotected trans diol [10,11]. Therefore, L-xylose glycoside **9** was treated with DAST to afford the fluorinated product in 54% yield. In agreement with the literature [6,7], we observed the regioselective formation of 3-fluoro-L-ribofuranoside **10**. Compound **10** was then treated with sulfuric acid in a mixture of acetic anhydride and acetic acid. In the next step, the 1-*O*-acetyl derivative was converted to phosphonate using the Vorbrüggen reaction in the presence of diisopropyl trimethylsilyloxymethylphosphonate. In our case, the reaction using silylated hydroxymethylphosphonate afforded improved yield of the glycosidation reaction over the reaction performed in the presence of hydroxymethylphosphonate [7]. Afterwards, the acyl groups were removed under basic conditions to afford phosphonate **12**. The next goal was to prepare a precursor with free primary hydroxyl. Therefore, we protected the primary hydroxyl with the dimethoxytrityl group and the secondary hydroxyl with benzoyl, and we then deprotected the primary hydroxyl with TFA to obtain the precursor **13**. In the next steps, we transformed the hydroxymethyl group to acetate, which was then used for the nucleosidation step [7]. Specifically, the hydroxymethyl group of the compound **13** was oxidized to the carboxylate **14** using (diacetoxyiodo)benzene in the presence of TEMPO**,** followed by oxidative decarboxylation using lead tetraacetate to yield acetate **15**. This precursor could be used for a nucleosidation reaction under the Vorbrüggen conditions. The precursor **15** was treated with silylated 6-*N*-benzoyladenine in the presence of tin tetrachloride. Because of the absence of the directing 2-*O*-acyl group, the reaction resulted in a mixture of β and α anomers in a 2:1 ratio, resp. The mixture was separated on a silica gel, and the desired β-anomer **16a** was deprotected to yield the novel D-2′-fluorotetradialdose nucleoside phosphonate **5a** product. Using a similar approach with silylated 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine, we also prepared guanine derivative **5b** (Scheme 1, Fig. 2).



16a, 16c: B = 6-*N*-benzoyladenin-9-yl
16b, 16d: B = 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanin-9-yl

5a: B = adenin-9-yl
5b: B = guanin-9-yl

Scheme 1. Synthesis of 2′-fluorotetradialdose nucleoside phosphonates. Reagents and conditions: (a) HCl, MeOH, rt, 16 h, quant.; (b) *p*-Toluoyl chloride, pyridine, 0 °C to rt, 16 h, 48%; (c) DAST, MeCN, 0 °C to rt, 16 h, 54%; (d) H_2SO_4, Ac_2O, AcOH, 0 °C to rt, 2 h, 84%; (e) hexamethyldisilazane, $(iPrO)_2P(O)CH_2OH$, saccharine, 100 °C, 8 h; (f) $SnCl_4$, MeCN, 55 °C, 1 h; (g) $MeNH_2$, EtOH, rt, 16 h, 85%; (h) DMTrCl, pyridine, rt, 16 h; (i) BzCl, DMAP, pyridine, rt, 8 h; (j) TFA, DCM, rt, 10 min, 74%; (k) $PhI(OAc)_2$, TEMPO, MeCN, rt, 16 h, 90%; (l) $Pb(OAc)_4$, THF, rt, 16 h, 60%; (m) $SnCl_4$, DCE, BSA, *N*6-benzoyladenine, rt, 30 min 43%; (n) TMSBr, pyridine, rt, 8 h; (o) $MeNH_2$, EtOH, rt, 73%.



Scheme 2. Synthesis of tetradialdose nucleoside phosphonates. Reagents and conditions: (a) HCl, MeOH, rt, 16 h; (b) H_2SO_4, Ac_2O, AcOH, 0 °C to rt, 2 h; (c) hexamethyldisilazane, $(iPrO)_2P(O)CH_2OH$, saccharine, 100 °C, 8 h; (d) $SnCl_4$, MeCN, 55 °C, 1 h; (e) NH_3, MeOH, 90%; (f) TBDPSCl, imidazole, DMF, rt, 24 h; (g) BzCl, Et_3N, DMAP, DCM, rt, 2 h; (h) TBAF, THF, rt, 8 h; 78%; (i) $PhI(OAc)_2$,TEMPO, $MeCN/H_2O$, rt, 16 h; (j) $Pb(OAc)_4$, THF, rt, 16 h; 53% (k) $SnCl_4$, MeCN, BSA, *N*6-benzoyladenine, 50%; (l) TMSBr, pyridine, rt, 8 h; (m) $MeNH_2$, EtOH, rt, 80%.

2.2. Synthesis of D-tetradialdose nucleoside phosphonates

In our experiment, the synthetic sequence for the preparation of 2′-hydroxy compound **1** described by Kim et al. [5] failed to afford the guanine derivative **6a**. Therefore, we adapted a synthetic approach similar to the approach used for the 2′-fluoro nucleosides. Starting from L-ribose, we prepared D-nucleoside **1** and the new nucleosides **6a**-**6c** bearing guanine, 8-azaadenine and 8-azaguanine, resp. (Scheme 2, Fig. 2).

L-Tetraacetylribose **18** was phosphonylated using the Vorbrüggen reaction with diisopropyl trimethylsilyloxymethylphosphonate. Then, the acetyl groups were removed under basic conditions to afford the phosphonate **19**. Next, the primary hydroxyl was protected with the TBDPS group, and cis diol was protected with the benzoyl groups. The TBDPS group was subsequently removed using TBAF to obtain the phosphonate **20**. The hydroxymethyl group was converted to acetate **21** using the above-mentioned sequence. A nucleosidation reaction using the Vorbrüggen reaction, silylated 6-*N*-benzoyladenine and 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine afforded compounds **22a** and **22b** as adenin-9-yl and guanin-9-yl β-anomers in good yields. After deprotection, compounds **1** and **6a** were obtained.

In contrast, in the case of the 8-azaadenine derivative, we observed the formation of 8-azaadenin-7-yl, 8-azaadenin-8-yl and 8-azaadenin-9-yl regioisomers during the Vorbrüggen reaction. Thus, the nucleosidation of acetate **21** with 8-azaadenine afforded a mixture of three regioisomers **23**, **24** and **25** in a 2:1:6 ratio (Scheme 2, Fig. 3). It is worth noting that the nucleosidation using silylated 8-azaadenine afforded the undesired regioisomer **24** as the only product. Regioisomer **24** was separated easily on a silica gel. Unfortunately, we were not able to separate the mixture of regioisomers **23** and **25** (in ratio 1:3), either on a silica gel or by using reverse phase chromatography. Therefore, we took advantage of the reported difference in the stability of the regioisomers of 8-azaadenosine under acidic conditions. It has been shown that the *N*7-regioisomer of 2′-deoxy-8-azaadenosine was hydrolyzed 75 times faster than the *N*9-regioisomer [12]. As an analogy, we exploited this phenomena to depurinate undesired *N*7-regioisomer **25**. First, we treated the mixture of compounds **23** and **25** with ammonia in methanol to remove the benzoyl groups, and then

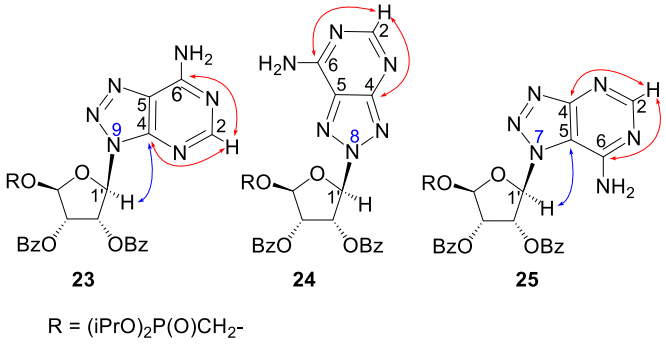
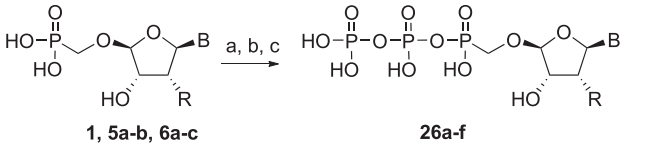


Fig. 3. Assignment of the structure of 8-azaadenine derivatives.

treated it with 80% AcOH until the *N*7-regioisomer depurinated. The *N*9-regioisomer **22c** was then easily purified on reverse phase, affording the desired 8-azaadenin-9-yl derivative as a β-anomer. After the final cleavage of protecting groups, compound **6b** was obtained (Scheme 2).

We performed NMR study to assign the structures of *N*9-, *N*8- and *N*7-regioisomers **23**, **24** and **25** (Fig. 3). These regioisomers could be distinguished on the basis of long-range C,H couplings observed in the 2D-H,C-HMBC spectra. The only C–H proton of 8-azaadenine, proton H-2, has long-range couplings with carbon C-4 and C-6 in all three regioisomers *N*9, *N*8 and *N*7 (see red arrows in **23**, **24** and **25** in Fig. 3). However, ribose proton H-1′ showed coupling to carbon C-4 in the *N*9-regioisomer, and coupling to C-5 in the *N*7-regioisomer (see blue arrows in **23** and **25** in Fig. 3), while it had no coupling to base carbons in the *N*8-regioisomer (proton H-1′ is separated by four bonds from both C-4 and C-5).

In the case of the 8-azaguanine derivative, we obtained the desired *N*9-regioisomer using the nucleosidation reaction in the presence of silylated 8-azaguanine (Scheme 2). The nucleosidation of acetate **21** afforded only two regioisomers. The 8-azaguanin-9-yl (**22d**) and 8-azaguanin-7-yl (**22e**) were obtained in a 1:5 ratio. The regioisomers were easily separated on a silica gel. Finally, the compound **22d** was deprotected to afford nucleotide **6c**. The structure of the regioisomers was assigned based on the 2D-H,C-HMBC spectra, as in case of 8-azaadenine derivative **6b**.



5a: B = adenin-9-yl, R = F
5b: B = guanin-9-yl, R = F
1: B = adenin-9-yl, R = OH
6a: B = guanin-9-yl, R = OH
6b: B = 8-azaadenin-9-yl, R = OH
6c: B = 8-azaguanin-9-yl, R = OH

26a: B = adenin-9-yl, R = F
26b: B = guanin-9-yl, R = F
26c: B = adenin-9-yl, R = OH
26d: B = guanin-9-yl, R = OH
26e: B = 8-azaadenin-9-yl, R = OH
26f: B = 8-azaguanin-9-yl, R = OH

Scheme 3. Synthesis of nucleoside phosphonodiphosphates. Reagents and conditions: (a) Imidazole, trioctylamine, PPh_3, Aldrithiol™, DMF, 16 h, rt; (b) tributylammonium pyrophosphate, DMF, 16 h, rt; (c) Dowex® 50 (Na^+ cycle), 45%.

2.3. Synthesis of nucleoside phosphonodiphosphates

Next, we continued with the preparation of nucleoside phosphonodiphosphates. The tetrabutylammonium salts of the phosphonic acids **5a-5b**, **1** and **6a-6c** were converted to the corresponding phosphonoimidazolide using PPh_3, imidazole and Aldrithiol™ [13]. Afterwards the imidazolides were converted to the corresponding phosphonodiphosphates **26a-f** using tributylammonium salt of pyrophosphate, and finalized as sodium salts (Scheme 3). The compound **26c** was already prepared and tested as a substrate of RNA polymerase *in vitro* assay by Koh et al. [14].

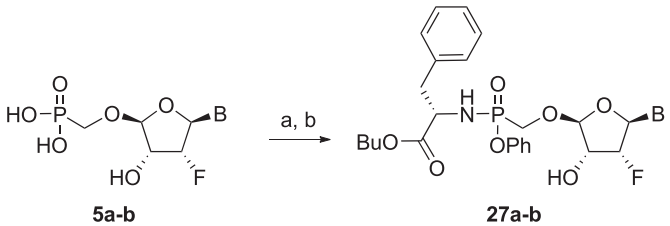
2.4. Synthesis of phosphoramidate prodrugs

The prodrug forms of the phosphonates **27a-27b** were prepared according to combined procedures of Klejch et al. [15] and Mackman et al. [16] (Scheme 4). We selected L-phenylalanine butyl ester phosphoramidates as a prodrug candidate based on the positive results of similar prodrug forms reported in the literature [17]. The phosphonic acids **5a-5b** were treated with L-phenylalanine butyl ester and phenol in the presence of triphenylphosphine and Aldrithiol™ to afford epimeric mixtures of the phosphoramidates in approximately a 1:1 ratio. Despite all efforts, we were not able to separate the epimeric mixtures, and therefore the phosphoramidate prodrugs were screened as a mixture of both epimers.

2.5. Biochemical evaluation

The phosphonodiphosphates **26a-26f** were tested for the inhibition of RNA template elongation by viral polymerases (RdRp) from Zika virus, HCV and Poliovirus, according to the conditions published previously [18,19]. Radioactivity based competition assay did not show any inhibition of these enzymes at a 20 μM concentration of phosphonodiphosphates **26a-26f**.

The potential antiviral effect of the prodrugs **27a-27b** was determined by screening against Coxsackie B3, Dengue 2, Influenza A, HIV-1 and Sars-CoV-2 viruses as published previously [20]. Unfortunately, the prodrugs showed low or no inhibition activity of these viruses.



5a: B = adenin-9-yl
5b: B = guanin-9-yl

27a: B = adenin-9-yl
27b: B = guanin-9-yl

Scheme 4. Synthesis of prodrugs. Reagents and conditions: (a) Phenol, L-phenylalanine butyl ester, Et_3N, pyridine, 15 min, 60 °C (b) PPh_3, Aldrithiol™, pyridine, 16 h, 60 °C, 56%.

3. Conclusion

We developed a synthetic route leading to the novel 2′-fluoro-D-tetraaldose nucleoside phosphonates and the synthesis of D-tetraaldose nucleoside phosphonates suitable for the preparation of tetraaldose nucleosides bearing purine nucleobases. These compounds were converted to appropriate phosphonodiphosphates and tested against viral polymerases from the Zika virus, HCV and Poliovirus. 2′-Fluoro nucleotides were also converted to prodrugs and screened against coxsackie, dengue, influenza, HIV-1 and Sars-CoV-2 viruses. Unfortunately, no biological activity was found. Nevertheless, the tetraaldose nucleoside phosphonates represent an interesting group of compounds and further exploration of its potential, e.g. synthesis of oligonucleotides bearing isosteric phosphonomethoxy linkages, is in progress.

4. Experimental section

Unless stated otherwise, all solvents used were anhydrous. Mass spectra were recorded on the ZAB-EQ (VG Analytical) instrument using FAB (ionization with Xe, accelerating voltage 8 kV; glycerol and thioglycerol as matrices) and on the LTQ Orbitrap XL (Thermo Fisher Scientific) using ESI ionization. The NMR spectra were measured on a Bruker AVANCE-600 instrument (^1H at 600.13 MHz and ^{13}C at 150.9 MHz) with a cryoprobe and a Bruker AVANCE-500 instrument with a cryoprobe (^{31}P at 202.4 MHz) in DMSO-d_6 and/or D_2O at 25 °C. The ^1H and ^{13}C spectra in DMSO were referenced to the solvent peak (using δ_H(DMSO) = 2.50 ppm; δ_C(DMSO) = 39.7 ppm) and spectra in D_2O were referenced to internal dioxane (using δ_H(dioxane) = 3.75 ppm; δ_C(dioxane) = 69.30 ppm). The ^{31}P spectra were referenced to external H_3PO_4. The structural assignment of the proton and carbon signals was achieved combining 1D-^1H and ^{13}C-spectra with homonuclear 2D-H,H—COSY, 2D-H,H-ROESY and heteronuclear 2D-H,C-HSQC and 2D-H,C-HMBC spectra. IR spectra were recorded on a Nicolet 6700 (Thermo Electron Corp.).

4.1. Methyl L-xylofuranoside (**8**)

A solution of acetyl chloride (5 mL; 70 mmol) and dry MeOH (100 mL) was added dropwise to a suspension of L -xylose 7 (100 g; 0.66 mol) in dry MeOH (1.2 L), and the reaction mixture was vigorously stirred for 16 h at room temperature. When the solution became homogenous, Dowex® 1 × 4 (OH^- cycle) was added until its pH became neutral. The resin was filtered, and the reaction mixture was concentrated. Methyl L-xylofuranoside 8 (112 g, quant. yield) was obtained as a colorless viscous oil, and was used in the next step without further purification.

4.2. Methyl 5-O-(4-methylbenzoyl)-L-xylofuranoside (**9**)

p-Toluoyl chloride (88 mL; 0.66 mol) in 200 mL of dry pyridine was added dropwise to a solution of methyl L-xylofuranoside 8 (112 g; 0.66 mol) in dry pyridine (500 mL) at 0 °C. The reaction mixture was warmed to room temperature, stirred for 16 h, then quenched by the addition of 50 mL of water, evaporated and extracted (1 L EtOAc/500 mL NaCl and 2 × 500 mL $NaHCO_3$). The

organic phase was dried over $MgSO_4$, and product **9** was isolated by chromatography on a silica gel (0–100% EtOAc in toluene) affording 90 g (48% over two steps) as a colorless viscous oil. Compound 9 was characterized by low resolution mass spectrometry: $(M + H)^+$ for $C_{14}H_{19}O_6$ calculated: 283.1; measured: 283.1.

4.3. Methyl 3-deoxy-3-fluoro-5-O-(4-methylbenzoyl)-L-xylofuranoside (**10**)

DAST (135 mL, 0.96 mol) diluted with 300 mL of ACN was added dropwise to a solution of compound **9** (90 g, 0.32 mol) in ACN (1 L). The reaction mixture was warmed to room temperature and stirred for 16 h. Next, 100 mL of water was added. The reaction mixture was evaporated and extracted (1 L toluene/500 mL sat. NaCl and 2 × 500 mL of sat. $NaHCO_3$). The organic phase was dried over $MgSO_4$, and product **10** was isolated by chromatography on a silica gel (0–60% EtOAc in cyclohexane) as a mixture of both anomers in a yield of 49 g (54%) of colorless viscose oil. Alpha anomer: HRMS $(M + Na)^+$ for $C_{14}H_{17}O_5FNa$ calculated: 307.09522; measured: 307.09492; IR (coating, cm^{-1}): 2841, 1720, 1612, 1450, 1380, 1272, 1179, 1074, 1020, 790, 752, 691, 475. For NMR data, see table Ia and Ib.

Beta anomer: HRMS $(M + Na)^+$ for $C_{14}H_{17}O_5FNa$ calculated: 307.09522; measured: 307.09494; IR (coating, cm^{-1}): 2841, 1720, 1612, 1450, 1380, 1272, 1179, 1074, 1020, 790, 752, 691, 475. For NMR data, see table Ia and Ib.

4.4. 1,2-Di-O-acetyl-3-deoxy-3-fluoro-5-O-(4-methylbenzoyl)-L-xylofuranose (**11**)

H_2SO_4 (1 mL), diluted with 20 mL of Ac_2O, was added dropwise to a solution of compound **10** (49 g; 172 mmol) in AcOH (80 mL) and Ac_2O (160 mL). The mixture was stirred at room temperature for 2 h, and then treated with water (200 mL). Then, the reaction mixture was neutralized with 10 g of $NaHCO_3$ and concentrated. The crude mixture was extracted (1 L DCM/500 mL sat. NaCl and 2 × 500 mL of sat. $NaHCO_3$). The organic phase was dried over $MgSO_4$, and product **11** was isolated by chromatography on a silica gel (0–10% EtOAc in toluene) as a mixture of both anomers in a yield of 51 g (84%). HRMS $(M + Na)^+$ for $C_{17}H_{19}O_7FNa$ calculated: 377.10070; measured: 377.10126; IR (coating, cm^{-1}): 1751, 1723, 1612, 1454, 1374, 1310, 1274, 1239, 1179, 1109, 1061, 1047, 883, 790, 667, 602, 474. For NMR data, see table Ia and Ib.

4.5. Diisopropylphosphonomethyl 3-deoxy-3-fluoro-β-L-ribofuranoside (**12**)

Hexamethyldisilazane (100 mL) and a catalytic amount of saccharin were added to diisopropyl (hydroxymethyl)phosphonate (30.4 g; 190 mmol), and the reaction mixture was stirred for 8 h at 100 °C. Hexamethyldisilazane was evaporated, and the residue was diluted with toluene and co-evaporated (3 × 100 mL). Then the compound **11** (34.4 g; 97 mmol) was added to silylated diisopropyl (trimethylsilyloxymethyl)phosphonate in ACN (1 L). Finally, $SnCl_4$ (24 mL; 200 mmol) was added. The reaction mixture was stirred for 1 h at 55 °C, quenched with 65 mL of pyridine, filtered and concentrated. Next, the crude mixture was dissolved in 800 mL of 33% $MeNH_2$ in EtOH, stirred for 8 h and concentrated. Product **12** was isolated by chromatography on a silica gel (0–10% EtOH in $CHCl_3$) in a yield of 26.9 g (84%). HRMS $(M + Na)^+$ for $C_{12}H_{24}O_7FNaP$ calculated: 353.11359; measured: 353.11368; IR (coating, cm-1): 3340, 1468, 1387, 1376, 1238, 1179, 1105, 1054, 999. For NMR data, see table Ia and Ib.

4.6. Diisopropylphosphonomethyl 2-O-benzoyl-3-deoxy-3-fluoro-β-L-ribofuranoside (**13**)

DMTr-Cl (14.2 g; 40 mmol) was added to a solution of phosphonate **12** (12.7 g; 38 mmol) in 400 mL of pyridine, and the reaction mixture was stirred at room temperature for 8 h. Next, BzCl (6.6 mL; 57 mmol) and DMAP (3 g; 24.6 mmol) were added. The reaction mixture was stirred for 8 h at room temperature, treated with water (100 mL), evaporated and extracted (1 L toluene/500 mL sat. NaCl and 2 × 500 mL of sat. NaHCO3). The organic phase was dried over $MgSO_4$, filtered, concentrated, diluted with 400 mL of dry DCM, and treated with TFA (5 mL) for 10 min at room temperature. The solution was neutralized by the addition of 20 mL of mixture MeOH/Et_3N (1:3) and concentrated. Product **13** was isolated by chromatography on a silica gel (0–90% EtOAc in toluene) in a yield of 12.2 g (74%). HRMS $(M + Na)^+$ for $C_{19}H_{28}O_8FNaP$ calculated: 457.13980; measured: 457.13949; IR (coating, cm-1): 3372, 2981, 1730, 1602, 1585, 1491, 1452, 1387, 1376, 1316, 1273, 1179, 1142, 1062, 998, 891, 857, 713, 673. For NMR data, see table Ia and Ib.

4.7. (2S,3R,4R,5R)-4-(benzoyloxy)-5-((diisopropoxyphosphoryl) methoxy)-3-fluorotetrahydrofuran-2-carboxylic acid (**14**)

BAIB (18 g; 56 mmol) and a catalytic amount of TEMPO were added to a solution of **13** (12.2 g; 28 mmol) in 50% ACN/water, and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of 100 mL of EtOH, concentrated and adsorbed onto a silica gel. Product **14** was isolated by chromatography on a silica gel (0–100% EtOAc in cyclohexane), and then eluted by 20% MeOH in $CHCl_3$ in a yield of 12.5 g (quantitative). HRMS $(M + Na)^+$ for $C_{19}H_{26}O_9FNaP$ calculated: 471.11907; measured: 471.11857; IR (coating, cm^{-1}): 3159, 2591, 1732, 1695, 1602, 1583, 1452, 1416, 1388, 1377, 1316, 1276, 1270, 1179, 1105, 1006, 938, 893, 850, 712, 677. For NMR data, see table Ia and Ib.

4.8. (2R,3R,4R)-5-acetoxy-2-((diisopropoxyphosphoryl)methoxy)-4-fluorotetrahydrofuran-3-yl benzoate (**15**)

$Pb(OAc)_4$ (25 g, 56 mmol) was added to a solution of **14** in THF (300 mL), and the reaction mixture was stirred for 8 h at room temperature. The resulting suspension was filtered and concentrated, and the acetate **15** was isolated by chromatography on a silica gel (0–50% EtOAc in toluene) in a yield of 7.8 g (60%). HRMS $(M + Na)^+$ for $C_{20}H_{28}O_9FNaP$ calculated: 485.13472; measured: 485.13416; IR (coating, cm^{-1}): 2981, 1755, 1733, 1602, 1585, 1493, 1453, 1386, 1376, 1317, 1272, 1246, 1179, 1106, 1025, 1006, 990, 889, 846, 713, 673, 603. For NMR data, see table Ia and Ib.

4.9. (2R,3R,4R,5R)-5-(6-benzamido-9H-purin-9-yl)-2-((diisopropoxyphosphoryl)methoxy)-4-fluorotetrahydrofuran-3-yl benzoate (**16a**)

Bis(trimethylsilyl)acetamide (7.3 mL; 30 mmol) was added to *N*-benzoyladenine (3.1 g; 13 mmol) in 1,2-dichloroethane (100 mL), and the reaction mixture was stirred for 1 h at 60 °C. The mixture was concentrated, co-evaporated with dry toluene (2 × 50 mL), added to the acetate **15** (3 g, 6.5 mmol) in 1,2-dichloroethane (100 mL) and finally $SnCl_4$ (6 mL; 52 mmol) was added. The reaction was stirred for 1 h at room temperature. Next, it was cooled in ice bath, quenched by the addition 16 mL of pyridine, filtered and concentrated. The reaction afforded mixture of compounds **16a** and **16c** in a 2:1 ratio. The product **16a** was isolated by chromatography on a silica gel (25–35% acetone in toluene) in a yield of 1.8 g (43%) as a faster eluting isomer. HRMS $(M + Na)^+$ for $C_{30}H_{33}O_8N_5FNaP$ calculated: 664.19430; measured: 664.19346; IR (coating, cm-1):

3068, 3032, 1700, 1603, 1582, 1512, 1490, 1452, 14101335, 1317, 1274, 1247, 1220, 1178, 1119, 1106,1080, 1031, 989, 904, 853, 797, 754, 711, 687, 646, 506. For NMR data, see table IIa and IIb.

4.10. (2R,3R,4R,5R)-5-(2-acetamido-6-((diphenylcarbamoyl)oxy)-9H-purin-9-yl)-2-((diisopropoxyphosphoryl)methoxy)-4-fluorotetrahydrofuran-3-yl benzoate (**16b**)

Nucleoside phosphonate **16b** was prepared according to the synthesis of compound **16a,** starting from the acetate **15** (2 g; 4.33 mmol) and *N*2-acetyl-*O*6-(diphenylcarbamoyl)guanine (550 mg; 1.4 mmol). The reaction afforded a mixture of compounds **16b** and **16d** in a 1:1 ratio. Compound **16b** was isolated in a yield of 662 mg (19%) as a faster eluting isomer. HRMS $(M + Na)^+$ for $C_{38}H_{40}O_{10}N_6FNaP$ calculated: 813.24198; measured: 813.24189; IR (coating, cm^{-1}): 3219, 3094, 3065, 3040, 2980, 2873, 1738, 1696, 1622, 1591, 1525, 1492, 1452, 1412, 1387, 1374, 1335, 1271, 1249, 1170, 1107, 989, 713, 700. For NMR data, see table IIa and IIb.

Table Ia
^{1}H NMR data of compounds **10**–**15** and **19**–**21**.[k]

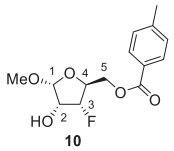
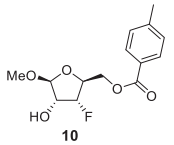
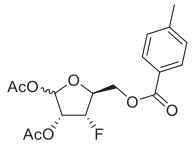
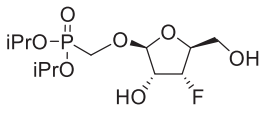
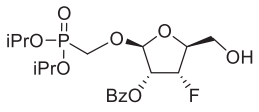
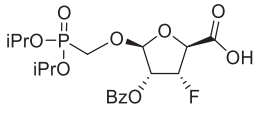
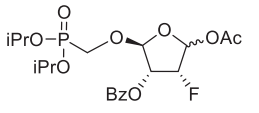
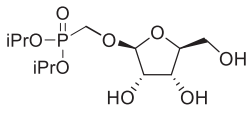
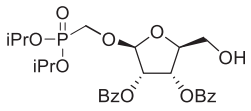
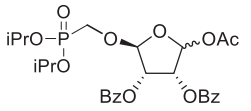
Compound	Solvent	H-1	H-2	H-3	H-4	H-5a; H-5b
 **10** (alpha-anomer)	DMSO [a]	4.86 d *1,2 = 4.7*	4.045 bdq *2,1 = 4.7* *2,F = 26.5 2, OH = 7.5* *2,3 = 5.5*	4.91 ddd *3,F = 56.2 3,2 = 5.5* *3,4 = 1.4*	4.44 dtd *4,F = 26.6* *4,5b = 4.4* *4,5a = 3.9* *4,3 = 1.4*	4.38 dd *5a, 5b = 11.8; 5a,4 = 3.9* 4.35 dd *5b, 5a = 11.8; 5b,4 = 4.4*
 **10** (beta-anomer)	DMSO [b]	4.77 t *1,2 = 2.0* *1,F = 2.0*	4.06 um	5.08 dt *3,F = 53.7* *3,2 = 4.5* *3,4 = 4.5*	4.42 m	4.44 m 4.30 m
 **11** alpha + beta anomer (56:44)	DMSO [c]	6.09 d *1,2 = 2.6* *1,F = 1.4* 6.39 d *1,2 = 4.8*	5.36 ddd *2,F = 11.0* *2,3 = 4.8* *2,1 = 2.6* 5.20 dt *2,F = 25.1* *2,3 = 5.2* *2,1 = 4.8*	5.52 ddd *3,F = 52.0 3,2 = 4.8* *3,4 = 3.8* 5.37 ddd *3,F = 55.0* *3,2 = 5.2* *3,4 = 1.3*	4.65 dq *4,F = 20.9* *4,5b = 4.2* *4,3 = 3.8* *4,5a = 3.6* 4.76 dtd *4,F = 26.7* *4,5b = 4.2* *4,5a = 3.7* *4,3 = 1.3*	4.56 dd *5a, 5b = 12.2; 5a,4 = 3.6* 4.39 dd *5b, 5a = 12.2; 5b,4 = 4.2* 4.44 dd *5a, 5b = 12.0; 5a,4 = 3.7* 4.42 dd *5b, 5a = 12.0; 5b,4 = 4.2*
 **12**	DMSO [d]	4.905 dd *1,2 = 2.6*	4.03 dddd *2,1 = 2.6* *2,3 = 4.4* *2, OH = 5.7* *2,F = 11.7*	4.86 dt *3,2 = 4.4* *3.F = 53.9* *3,4 = 3.8*	4.08 dtd *4,3 = 3.8* *4,F = 20.9* *4,5a = 5.5* *4,5b = 5.5*	3.45 m (2H)
 **13**	DMSO [e]	5.40 dd *1,2 = 3.1* *1,F = 1.4*	5.31 ddd *2,1 = 3.1* *2,3 = 4.9* *2,F = 11.7*	5.30 ddd *3,2 = 4.9* *3.F = 53.6* *3,4 = 3.1*	4.29 dtd *4,3 = 3.1* *4,F = 22.6* *4,5a = 5.4* *4,5b = 5.0*	3.57 m (2H)
 **14**	DMSO [f]	5.47 dd *1,2 = 2.4* *1,F = 1.3*	5.34 ddd *2,1 = 2.4* *2,3 = 4.7* *2,F = 9.4*	5.53 ddd *3,2 = 4.7* *3.F = 52.6* *3,4 = 3.4*	4.77 dd *4,3 = 3.4* *4,F = 23.2*	–
 **15** beta and alpha epimers (83:17)	DMSO [g] *data for major β-epimer only*	5.65 d *1,2 = 3.1*	5.38 ddd *2,1 = 3.1* *2,3 = 4.4* *2,F = 17.0*	5.44 ddd *3,2 = 4.4* *3.F = 50.5* *3,4 = 1.2*	6.31 dd *4,3 = 1.2* *4,F = 10.8*	–
 **19**	DMSO [h]	4.80 s *1,2 = 0*	3.74 bd *2,1 = 0* *2,3 = 4.6*	3.87 dd *3,2 = 4.6* *3,4 = 7.2*	3.78 ddd *4,3 = 7.2* *4,5a = 3.2* *4,5b = 6.1*	3.54 dd *5a, 5b = 11.8; 5a,4 = 3.2* 3.34 dd *5b, 5a = 11.8; 5b,4 = 4.4*

Table Ia (*continued*)

Compound	Solvent	H-1	H-2	H-3	H-4	H-5a; H-5b
 **20**	DMSO [i]	5.38 d *1,2 = 1.5*	5.51 dd *2,1 = 1.5* *2,3 = 5.0*	5.54 dd *3,2 = 5.0* *3,4 = 5.8*	4.42 ddd *4,3 = 5.8* *4,5a = 4.6* *4,5b = 5.1*	3.68 ddd *5a, 5b = 12.0; 5a,4 = 4.6* *5a, OH = 5.8* 3.61 ddd *5b, 5a = 12.0; 5b,4 = 5.1* *5b, OH = 6.0*
 **21**	DMSO [j]	5.65 d *1,2 = 2.1* 5.64 d *1,2 = 0.9*	5.60 dd *2,1 = 2.1* *2,3 = 5.1* 5.59 dd *2,1 = 0.9* *2,3 = 5.1*	5.67 dd *3,2 = 5.1* *3,4 = 2.4* 5.67 dd *3,2 = 5.1* *3,4 = 4.9*	6.46 d *4,3 = 2.4* 6.60 d *4,3 = 4.9*	– –

beta and alpha epimers (76:24)

[a] **1-OMe**: 3.33 s; **2-OH**: 5.12 br; **5-OTol**: 7.84 m (2x *o*-ArH), 7.35 m (2x *m*-ArH), 2.385 s (CH_3).

[b] **1-OMe**: 3.22 s; **2-OH**: 5.70 br; **5-OTol**: 7.88 m (2x *o*-ArH), 7.35 m (2x *m*-ArH), 2.38 s (CH_3).

[c] **α-anomer: 1-OAc:** 1.88 s**; 2-OAc**: 2.13 s; **5-OTol**: 7.92 m (2x *o*-ArH), 7.36 m (2x *m*-ArH), 2.39 s (CH_3); **β-anomer: 1-OAc:** 2.07 s**; 2-OAc**: 2.12 s; **5-OTol**: 7.87 m (2x *o*-ArH), 7.34 m (2x *m*-ArH), 2.39 s (CH_3).

[d] **2-OH**: 5.66 bd, *J = 5.7* Hz; **5-OH**: 4.96 bt, *J = 5.5* Hz; **O–CH_2–P = O(OiPr)$_2$**: 3.84 dd, *J = 13.8, 9.0* Hz and 3.73 dd, *J = 13.8, 9.1* Hz (P–CH_2–O), 4.59 m, 2H, 1.235 d, *J = 6.2* Hz, 1.237 d, *J = 6.2* Hz, 1.244 d, *J = 6.2* Hz and 1.246 d, *J = 6.2* Hz (2x OiPr).

[e] **2-OBz**: 8.01 m (2x *o*-ArH), 7.57 m (2x *m*-ArH), 7.71 m (*p*-ArH); **5-OH**: 5.14 bt, *J = 5.6* Hz; **O–CH_2–P = O(OiPr)$_2$**: 3.95 dd, *J = 13.9, 9.0* Hz and 3.87 dd, *J = 13.9, 8.9* Hz (P–CH_2–O), 4.69 m, 2H, 1.213 d, 3H, *J = 6.2* Hz, 1.218 d, 3H, *J = 6.2* Hz, 1.223 d, 3H, *J = 6.2* Hz and 1.231 d, 3H, *J = 6.2* Hz (2x OiPr).

[f] **2-OBz**: 8.00 m (2x o-ArH), 7.57 m (2x *m*-ArH), 7.71 m (*p*-ArH); **O–CH_2–P = O(OiPr)$_2$**: 4.06 dd, *J = 13.8, 8.2* Hz and 3.92 dd, *J = 13.8, 9.4* Hz (P–CH_2–O), 4.59 m, 2H, 1.210 d, 6H, *J = 6.2* Hz, 1.221 d, 3H, *J = 6.2* Hz, 1.225 d, 3H, *J = 6.2* Hz (2x OiPr).

[g] **2-OBz**: 8.02 m (2x *o*-ArH), 7.58 m (2x *m*-ArH), 7.73 m (*p*-ArH); **4-OAc**: 2.10 s; **O–CH_2–P = O(OiPr)$_2$**: 3.92 m, 2H (P–CH_2–O), 4.60 m, 2H, 1.205 d, 3H, *J = 6.0* Hz, 1.213 d, 3H, *J = 6.2* Hz, 1.216 d, 3H, *J = 6.0* Hz and 1.231 d, 3H, *J = 6.1* Hz (2x OiPr).

[h] **O–CH_2–P = O(OiPr)$_2$**: 3.84 dd, *J = 13.8, 8.9* Hz and 3.65 dd, *J = 13.8, 8.7* Hz (P–CH_2–O), 4.58 m, 2H, 1.245 d, 3H, *J = 6.2* Hz, 1.242 d, 3H, *J = 6.2* Hz and 1.234 d, 6H, *J = 6.6* Hz (2x OiPr).

[i] **2-OBz**: 7.87 m (2x *o*-ArH), 7.47 m (2x *m*-ArH), 7.65 m (*p*-ArH); **3-OBz**: 7.85 m (2x *o*-ArH), 7.44 m (2x *m*-ArH), 7.62 m (*p*-ArH); **5-OH**: 5.08 t, *J = 5.8* and 6.0 Hz; **O–CH_2–P = O(OiPr)$_2$**: 4.00 dd, *J = 13.8, 9.0* Hz and 3.87 dd, *J = 13.8, 8.9* Hz (P–CH_2–O), 4.64 m, 2H, 1.260 d, 6H, *J = 6.2* Hz, 1.264 d, 3H, *J* = 6.2 Hz and 1.268 d, 3H, *J = 6.2* Hz (2x OiPr).

[j] **Major epimer: 2-OBz**: 7.88 m (2x *o*-ArH), 7.465 m (2x m-ArH), 7.655 m (*p*-ArH); **3-OBz**: 7.88 m (2x *o*-ArH), 7.465 m (2x *m*-ArH), 7.655 m (*p*-ArH); **O–CH_2–P = O(OiPr)$_2$**: 3.95 dd, *J = 13.7, 9.0* Hz and 3.92 dd, *J = 13.7, 9.3* Hz (P–CH_2–O), 4.64 m, 2H, 1.250 d, 3H, *J = 6.2* Hz, 1.260 d, 3H, *J = 6.2* Hz, 1.266 d, 3H, *J = 6.2* Hz and 1.270 d, 3H, *J = 6.2* Hz (2x OiPr); **4-OAc**: 2.13 s; **minor epimer: 2-OBz**: 8.005 m (2x *o*-ArH), 7.565 m (2x *m*-ArH), 7.705 m (*p*-ArH); **3-OBz**: 7.76 m (2x *o*-ArH), 7.42 m (2x *m*-ArH), 7.62 m (*p*-ArH); **O–CH_2–P = O(OiPr)$_2$**: 3.99 dd, *J = 13.7, 9.0* Hz and 3.96 dd, *J = 13.7, 8.7* Hz (P–CH_2–O), 4.64 m, 2H, 1.252 d, 6H, *J = 6.2* Hz, 1.273 d, 3H, *J = 6.2* Hz and 1.277 d, 3H, *J = 6.2* Hz (2x OiPr).

[k] Coupling constants are written in italics in a shortened form (e.g. instead *J(1',2') = 8.6* Hz we type simply *1,2 = 8.6*).

*4.11. (2R,3R,4R,5S)-5-(6-benzamido-9H-purin-9-yl)-2-((diisopropoxyphosphoryl)methoxy)-4-fluorotetrahydrofuran-3-yl benzoate (**16c**)*

Nucleoside phosphonate **16c** was prepared as a side product of the preparation of nucleoside phosphonate **16a**.

Alpha anomer was isolated as a slower eluting isomer in a yield of 980 mg (23%). HRMS $(M + Na)^+$ for $C_{30}H_{33}O_8N_5FNaP$ calculated: 664.19430; measured: 664.19348; IR (coating, cm^{-1}): 3416, 3238, 3164, 3064, 2980, 2934, 2875, 1733, 1700, 1603, 1583, 1511, 1490, 1452, 1386, 1375, 1340, 1316, 1296, 1275, 1252, 1178, 1118, 1105, 1080, 1027, 996, 904, 889, 798, 753, 710, 686, 644, 506. For NMR data, see table IIa and IIb.

*4.12. (2R,3R,4R,5S)-5-(2-acetamido-6-((diphenylcarbamoyl)oxy)-9H-purin-9-yl)-2-((diisopropoxyphosphoryl)methoxy)-4-fluorotetrahydrofuran-3-yl benzoate (**16d**)*

Nucleoside phosphonate **16d** was prepared as a side product of the preparation of phosphonate nucleoside **16b**. Alpha anomer was isolated in a yield of 430 mg (13%) as a slower eluting isomer. HRMS $(M + Na)^+$ for C38H40O10N6FNaP calculated: 813.24198; measured: 813.24215; IR (coating, cm-1): 3217, 3064, 2980, 2870, 2854, 1738, 1700, 1623, 1600, 1591, 1511, 1492, 1452, 1386, 1375, 1335, 1316, 1272, 1246, 1179, 1170, 1135, 1121, 1106, 1078, 1061, 1026, 1003, 991, 907, 889, 758, 713, 700, 695, 666, 641, 532, 510. For NMR data, see table IIa and IIb.

*4.13. ((((2R,3R,4R,5R)-5-(6-amino-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic acid (**5a**)*

Bromotrimethylsilane (410 μL; 3.1 mmol) was added to the phosphonate **16a** (200 mg; 0.31 mmol) in pyridine (5 mL), and the mixture was stirred for 8 h at room temperature and concentrated. The residue was diluted with saturated NH_3 in 50% MeOH/H_2O (20 mL), stirred for 16 h at room temperature, and then concentrate. The nucleotide **5a** was isolated by reverse phase chromatography (first 10 min of isocratic elution with 0.1 M TEAB, then 40 min gradient 0–15% MeOH in 0.1 M TEAB) in a yield of 100 mg (92%): HRMS $(M - H)^-$ for $C_{10}H_{12}O_6N_5FP$ calculated: 348.05147; measured: 348.05117; IR (KBr, cm_{-1}): 3388, 3273, 2755, 2679, 2530, 2492, 1687, 1642, 1575, 1474, 1421, 1296, 1245, 1212, 1087, 1050, 796, 720, 642. For NMR data, see table IIa and IIb.

*4.14. ((((2R,3R,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic acid (**5b**)*

The compound **5b** was prepared according to the synthesis of compound **5a,** starting from **16b** (586 mg; 0.74 mmol) in a yield of 229 mg (84%): HRMS $(M - H)^-$ for $C_{10}H_{12}O_7N_5FP$ calculated: 364.04639; measured: 364.04587; IR (coating, cm^{-1}): 3466, 3129, 2958, 2934, 2874, 2743, 1693, 1654, 1610, 1532, 1488, 1467, 1377, 1142, 1106, 1068, 889, 796, 779, 688. For NMR data, see table IIa and IIb.

4.15. 1,2,3,5-Tetraacetyl-L-ribofuranose (**18**)

Acetyl chloride (3.5 mL; 50 mmol) in 100 mL of dry MeOH was added to a solution of L-ribose 17 (100 g; 0.67 mol) in dry MeOH (1200 mL), and the reaction mixture was stirred for 16 h at 4 °C. Afterwards, it was filtered through the column of Dowex® 1 × 4 (150 mL; OH^- cycle) and evaporated. The crude mixture was diluted with dioxane and co-evaporated (3 × 100 mL). H_2SO_4 (3 mL; 56 mmol) in Ac_2O (20 mL) was added dropwise to the solution of crude methyl L-ribofuranoside in AcOH (250 mL) and Ac_2O (500 mL) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. Next, the reaction was quenched by the

Table Ib
^{13}C,^{31}P and^{19}F NMR data of compounds **10**–**15** and **19**–**21** [k]

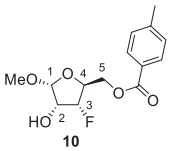
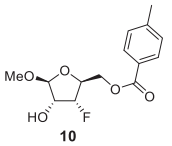
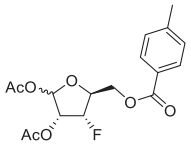
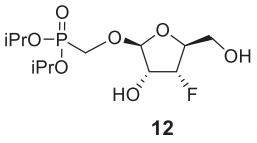
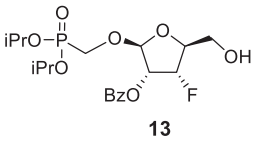
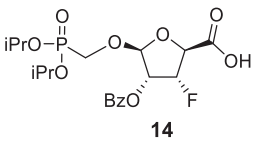
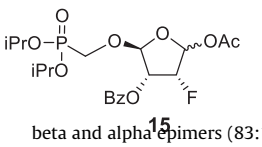
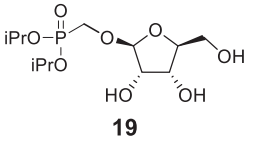
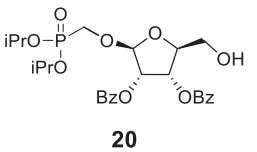
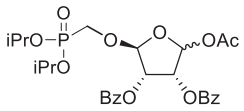
Compound	Solvent	C-1	C-2	C-3	C-4	C-5	^{31}P	^{19}F
 **10** (alpha-anomer)	DMSO [a]	102.64	71.74 *2,F = 16.4*	90.88 *3,F = 185.2*	80.09 *4,F = 24.8*	64.09 *5,F = 10.3*	–	−189.10
 **10** (beta-anomer)	DMSO [b]	108.19 *1,F = 3.2*	73.35 *2,F = 15.0*	92.11 *3,F = 186.6*	78.47 *4,F = 25.0*	64.03 *5,F = 5.9*	–	−205.56
 **11** beta and alpha anomers (56:44)	DMSO [c] *β-epimer* *α-epimer*	98.20 *1,F = 1.9* 93.30	74.69 *2,F = 14.2* 71.00 *2,F = 14.7*	89.68 *3,F = 189.9* 88.84 *3,F = 188.1*	81.91 *4,F = 24.7* 81.09 *4,F = 24.8*	63.20 *5,F = 6.8* 63.63 *5,F = 10.1*	– –	−203.10 −190.71
 **12**	DMSO [d]	107.71 *1,P = 12.0* *1,F = 2.4*	73.56 *2,F = 15.3*	82.48 *3,F = 185.8*	82.32 *4,F = 22.2*	61.78 *5,F = 6.3*	20.56	−203.93
 **13**	DMSO [e]	105.30 *1,P = 12.2 1,F = 1.4*	75.56 *2,F = 14.2*	90.81 *3,F = 188.1*	83.40 *4,F = 21.9*	61.29 *5,F = 7.3*	19.95	−201.10
 **14**	DMSO [f]	105.47 *1,P = 12.1*	74.82 *2,F = 13.8*	92.21 *3,F = 193.1*	80.56 *4,F = 23.4*	170.81 *5,F = 9.2*	19.92	−199.95
 **15** beta and alpha epimers (83:17)	DMSO [g] *data for major β-epimer only*	107.10 *1,P = 13.4*	75.26 *2,F = 14.3*	91.96 *3,F = 188.8*	98.26 *4,F = 33.1*	–	18.98	−206.24
 **19**	DMSO [h]	107.73 *1,P = 11.6*	74.40	70.73	84.03	62.80	21.08	–
 **20**	DMSO [i]	105.23 *1,P = 12.2*	74.87	72.27	82.20	61.98	20.12	–

Table Ib (*continued*)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	^{31}P	^{19}F
 **21**	DMSO [j]	106.98	74.63	75.29	98.82	–	18.03	–
	β-epimer	*1,P = 13.1*						
	α-epimer	105.53	72.28	70.16	93.14	–	19.19	–
		1,P = 12.3						

beta and alpha epimers (76:24)

Substituents.

[a] **1-OMe:** 55.11; **2-OTol:** 165.61 (C=O), 126.77 (*i*-ArC), 129.43 (2x *o*-ArC), 129.61 (2x *m*-ArC), 144.11 (*p*-AQrC), 21.38 (CH_3).

[b] **1-OMe:** 55.16; **2-OTol:** 165.65 (C=O), 126.92 (*i*-ArC), 129.46 (2x *o*-ArC), 129.53 (2x *m*-ArC), 144.03 (*p*-ArC), 21.37 (CH_3).

[c] **α-anomer: 1-OAc:** 169.19 (C=O), 20.74 (CH_3); **2-OAc:** 169.53 (C=O), 20.48 (CH_3); **2-OTol:** 165.42 (C=O), 126.71 (*i*-ArC), 129.53 (2x *o*-ArC), 129.58 (2x *m*-ArC), 144.20 (*p*-ArC), 21.35 (CH_3); **β-anomer: 1-OAc:** 169.77 (C=O), 21.06 (CH_3); **2-OAc:** 169.73 (C=O), 20.40 (CH_3); **2-OTol:** 165.50 (C=O), 126.59 (*i*-ArC), 129.48 (2x *o*-ArC), 129.56 (2x *m*-ArC), 144.20 (*p*-ArC), 21.34 (CH_3).

[d] **O–CH_2–P = O(OiPr)$_2$**: 61.12 d, *J = 166.*9 Hz (P–CH_2–O), 70.70 d, *J = 5.*0 Hz and 70.57 d, *J = 5.*0 Hz (2x O–CH<), 23.93 d, *J = 4.*6 Hz (2x CH_3), and 24.06 d, *J = 3.*4 Hz (2x CH_3).

[e] **2-OBz:** 164.92 (C=O), 128.74 (*i*-ArC), 129.67 (2x *o*-ArC), 129.22 (2x *m*-ArC), 134.29 (*p*-ArC), **O–CH_2–P = O(OiPr)$_2$**: 61.46 d, *J = 166.*3 Hz (P–CH_2–O), 70.81 d, *J = 6.*3 Hz (2x O–CH<), 23.88 d, *J = 4.*6 Hz (CH_3), 23.87 d, *J = 4.*6 Hz (CH_3), 24.03 d, *J = 3.*7 Hz (CH_3) and 24.03 d, *J = 3.*7 Hz (CH_3).

[f] **2-OBz:** 164.82 (C=O), 128.61 (*i*-ArC), 129.68 (2x *o*-ArC), 129.19 (2x *m*-ArC), 134.30 (*p*-ArC), **O–CH_2–P = O(OiPr)$_2$**: 60.85 d, *J = 165.*6 Hz (P–CH_2–O), 70.77 d, *J = 6.*2 Hz and 70.80 d, *J = 6.*2 Hz (2x O–CH<), 23.82 d, *J = 4.*7 Hz (CH_3), 23.86 d, *J = 4.*7 Hz (CH_3), 23.97 d, *J = 3.*6 Hz (CH_3) and 24.00 d, *J = 3.*8 Hz (CH_3).

[g] **2-OBz:** 164.86 (C=O), 128.41 (*i*-ArC), 129.81 (2x *o*-ArC), 129.32 (2x *m*-ArC), 134.54 (*p*-ArC), **4-OAc:** 169.17 (C=O), 21.03 (CH_3); **O–CH_2–P = O(OiPr)$_2$**: 62.32 d, *J = 166.*0 Hz (P–CH_2–O), 70.95 d, *J = 6.*2 Hz and 70.93 d, *J = 6.*1 Hz (2x O–CH<), 23.87 d, *J = 4.*4 Hz (2x CH_3), 24.03 d, *J = 3.*5 Hz (2x CH_3).

[h] **O–CH_2–P = O(OiPr)$_2$**: 60.47 d, *J = 166.*9 Hz (P–CH_2–O), 70.46 d, *J = 6.*0 Hz and 70.42 d, *J = 6.*0 Hz (2x O–CH<), 24.02 d, *J = 4.*5 Hz (2x CH_3), 23.89 d, *J = 4.*8 Hz (2x CH_3).

[i] **2-OBz:** 164.73 (C=O), 128.88 (*i*-ArC), 129.43 (2x *o*-ArC), 129.01 (2x *m*-ArC), 134.09 (*p*-ArC), **3-OBz:** 165.06 (C=O), 128.73 (*i*-ArC), 129.37 (2x *o*-ArC), 128.92 (2x *m*-ArC), 133.94 (*p*-ArC); **O–CH_2–P = O(OiPr)$_2$**: 61.07 d, *J = 166.*6 Hz (P–CH_2–O), 70.71 d, *J = 6.*3 Hz (2x O–CH<), 23.86 d, *J = 4.*5 Hz (2x CH_3), 24.00 d, *J = 3.*7 Hz (2x CH_3).

[j] **Major β-epimer: 2-OBz:** 164.67 (C=O), 128.42 (*i*-ArC), 129.56 (2x *o*-ArC), 129.03 (2x *m*-ArC), 134.25 (*p*-ArC), **3-OBz:** 164.62 (C=O), 128.41 (*i*-ArC), 129.50 (2x *o*-ArC), 129.00 (2x *m*-ArC), 134.21 (*p*-ArC); **O–CH_2–P = O(OiPr)$_2$**: 61.88 d, *J = 166.*0 Hz (P–CH_2–O), 70.83 d, *J = 6.*2 Hz and 70.77 d, *J = 6.*2 Hz (2x O–CH<), 23.81 d, 2C, *J = 4.*6 Hz (2x CH_3), 23.96 d, *J = 3.*5 Hz and 23.97 d, *J = 3.*7 Hz (2x CH_3); **4-OAc**: 169.39 (C=O), 20.95 (CH_3); **minor α-epimer**: **2-OBz:** 164.70 (C=O), 128.83 (*i*-ArC), 129.54 (2x *o*-ArC), 129.14 (2x *m*-ArC), 134.23 (*p*-ArC), **3-OBz:** 164.46 (C=O), 128.44 (*i*-ArC), 129.28 (2x *o*-ArC), 129.03 (2x *m*-ArC), 134.15 (*p*-ArC); **O–CH_2–P = O(OiPr)$_2$**: 61.82 d, *J = 166.*1 Hz (P–CH_2–O), 70.83 d, *J = 6.*2 Hz and 70.77 d, *J = 6.*2 Hz (2x O–CH<), 23.98 d, *J = 3.*7 Hz (2x CH_3), 23.86 d, *J = 4.*6 Hz (CH_3) and 23.84 d, *J = 4.*6 Hz (CH_3); **4-OAc**: 169.27 (C=O), 20.85 (CH_3).

[k] Coupling constants are written in italics in a shortened form (e.g. instead *J(C2,F) = 16.*4 Hz we type simply *2,F = 16.4*).

addition of 100 mL of dry MeOH, and after 5 min of stirring, AcONa (6 g, 73 mmol) was added. The reaction product was evaporated, diluted with toluene (1 L) and washed with brine (500 mL) and sat. $NaHCO_3$ (aq., 500 mL). The organic layer was dried over $MgSO_4$, filtrated and evaporated. Crude acetate **18** was used for the next step without further purification.

4.16. Diisopropylphosphonomethyl β-L-ribofuranoside (**19**)

Hexamethyldisilazane (400 mL) and a catalytic amount of saccharin were added to diisopropyl (hydroxymethyl)phosphonate (137 g; 700 mmol), and the reaction mixture was stirred for 8 h at 100 °C. Hexamethyldisilazane was evaporated, and the silylated phosphonate was coevaporated with toluene (3 × 100 mL). The crude acetate **18** was added to the silylated phosphonate in dry ACN (1.5 L). Finally, $SnCl_4$ (100 mL; 850 mmol) was carefully added. The reaction mixture was stirred for 1 h at 55 °C, then quenched with 280 mL of pyridine, filtered and concentrated. Next, the crude mixture was dissolved in sat. NH_3 in MeOH (1 L), and stirred for 16 h at room temperature. Product **19** was isolated by chromatography on a silica gel (0–10% MeOH in $CHCl_3$) in a yield of 195 g (90% over 4 steps): HRMS $(M + Na)^+$ for $C_{12}H_{25}O_8NaP$ calculated: 351.11793; measured: 351.11835; IR ($CHCl_3$, cm^{-1}): 3355, 2981, 2934, 2878, 1467, 1454, 1387, 1376, 1234, 1180, 1104, 1054, 996, 891, 721. For NMR data, see table Ia and Ib.

4.17. Diisopropylphosphonomethyl 2,3-O-dibenzoyl-β-L-ribofuranoside (**20**)

TBDPSCl (20 mL; 77 mmol) was added dropwise to the solution of phosphonate **19** (22.7 g; 69 mmol) in dry pyridine (500 mL), and the reaction mixture was stirred for 16 h at room temperature. Next, Et_3N (20 mL; 140 mmol) and DMAP (1 g; 8 mmol) were added, followed by the dropwise addition of BzCl (17 mL; 140 mmol). The mixture was then stirred for another 8 h at room temperature. The reaction was quenched by the addition of water (50 mL), and concentrated. The residue was diluted with Et_2O (1 L), and extracted with a saturated solution of brine (500 mL) and sodium bicarbonate (2 × 500 mL). The organic phase was dried over Na_2SO_4, filtered, concentrated and dried by co-evaporation with toluene (3 × 100 mL). Next, the residue was diluted with THF (400 mL), TBAF × $3H_2O$ was added (25.3 g; 80 mmol), and the mixture was stirred for 1 h at room temperature. The reaction was quenched by the addition of 20 mL of water, concentrated, diluted with Et_2O (500 mL) and extracted between Et_2O and saturated aqueous NH_4Cl (3 × 300 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated. Product **20** was isolated by chromatography on a silica gel (0–50% EtOAc in toluene) in a yield of 28.85 g (78%): HRMS $(M + Na)^+$ for $C_{42}H_{51}O_{10}NaPSi$ calculated: 797.28813; measured: 797.28842; IR ($CHCl_3$, cm^{-1}): 2978, 2892, 1732, 1602, 1585, 1491, 1472, 1464, 1452, 1428, 1386, 1375, 1362, 1316, 1276, 1178, 1125, 1113, 1070, 1028, 991, 938, 889, 708, 615, 505. For NMR data, see table Ia and Ib.

4.18. (3R,4S,5R)-2-acetoxy-5-((diisopropoxyphosphoryl)methoxy) tetrahydrofuran-3,4-diyl dibenzoate (**21**)

2,2,6,6-Tetramethylpiperidine 1-oxyl (156 mg; 1 mmol) and (diacetoxyiodo)benzene (6.5 g; 20 mmol) were added to the phosphonate **20** (5.3 g; 10 mmol) in 30% water in ACN (100 mL), and the mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of 20 mL of EtOH, evaporated and co-evaporated with water (5 × 50 mL) and then with toluene (3 × 30 mL). The reaction intermediate was used in the next step without further purification.

$Pb(OAc)_4$ (5.5 g; 12.3 mmol) was added to crude carboxylic acid dissolved in 100 mL dry THF. The reaction mixture was stirred for 2 h at room temperature, filtered and concentrated. Product **21** was isolated by chromatography on a silica gel (0–30% EtOAc in toluene) in a yield of 2.95 g (53% over two steps): HRMS $(M + Na)^+$

Table IIa
^{1}H NMR data of compounds **5, 6, 16** and **22**–**27** [x]

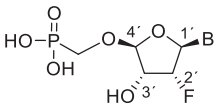
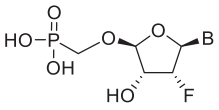
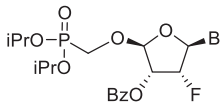
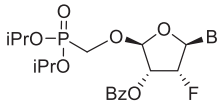
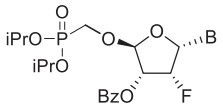
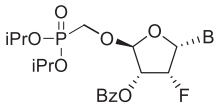
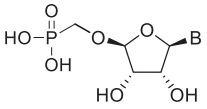
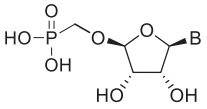
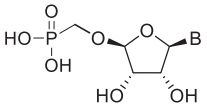
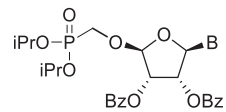
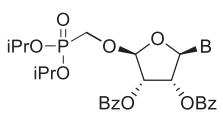
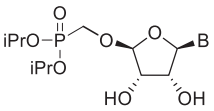
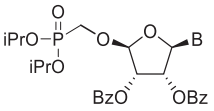
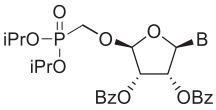
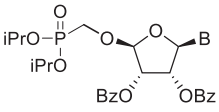
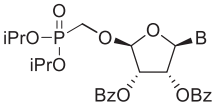
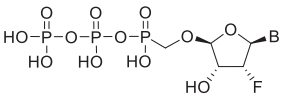
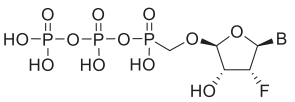
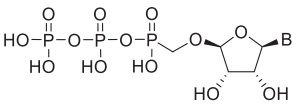
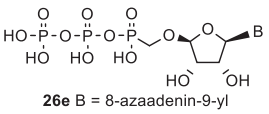
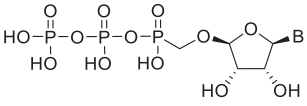
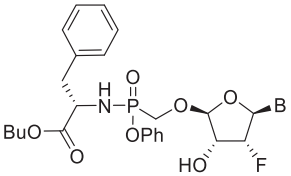
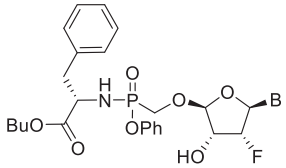
Compound	Solvent	H-1'	H-2'	H-3'	H-4'	Base
 **5a** B = Adenin-9-yl	D_2O [a]	6.44 dd *1,2 = 4.3* *1,F = 14.6*	5.71 dt *2,F = 50.8* *2,1 = 4.3* *2,3 = 4.4*	4.59 ddd *3,2 = 4.4* *3,F = 7.1* *3,4 = 2.0*	5.33 dd *4,3 = 2.0* *4,F = 1.7*	H-2: 8.15 s H-8: 8.33 s
 **5b** B = Guanin-9-yl	D_2O [b]	6.31 dd *1,2 = 4.2* *1,F = 15.4*	5.72 dt *2,F = 51.1* *2,1 = 4.2* *2,3 = 4.4*	4.62 ddd *3,2 = 4.4* *3,F = 8.1* *3,4 = 2.3*	5.32 dd *4,3 = 2.3* *4,F = 1.6*	H8: 8.06 s
 **16a** B = 6-*N*-benzoyladenin-9-yl	DMSO [c]	6.74 dd *1,2 = 3.6* *1,F = 17.0*	6.35 ddd *2,1 = 3.6* *2,F = 49.8* *2,3 = 4.9*	5.91 ddd *3,2 = 4.9* *3,F = 9.2* *3,4 = 2.5*	5.71 dd *4,3 = 2.5* *4,F = 1.0*	H-2: 8.80 s H-8: 8.65 s
 **16b** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [d]	6.59 dd *1,2 = 3.2* *1,F = 17.6*	6.31 ddd *2,1 = 3.2* *2,F = 49.9* *2,3 = 5.0*	6.02 ddd *3,2 = 5.0* *3,F = 10.3* *3,4 = 2.7*	5.70 dd *4,3 = 2.7* *4,F = 0.6*	H-8: 8.59 s
 **16c** B = 6-*N*-benzoyladenin-9-yl	DMSO [e]	6.995 dd *1,2 = 3.7* *1,F = 16.8*	5.79 ddd *2,1 = 3.7* *2,F = 52.2* *2,3 = 4.5*	5.72 ddd *3,2 = 4.5* *3,F = 15.3* *3,4 = 3.5*	5.95 dd *4,3 = 3.5* *4,F = 1.3*	H-2: 8.81 s H-8: 8.60 d *8,F = 2.7*
 **16d** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [f]	6.82 dd *1,2 = 3.8* *1,F = 16.2*	5.74 ddd *2,1 = 3.8* *2,F = 52.1* *2,3 = 4.7*	5.67 ddd *3,2 = 4.7* *3,F = 16.1* *3,4 = 3.9*	6.08 dd *4,3 = 3.9* *4,F = 1.2*	H-8: 8.55 d *8,F = 2.5*
 **6a** B = guanin-9-yl	D_2O [g]	6.02 d *1,2 = 6.5*	4.97 ddd *2,1 = 6.5* *2,3 = 4.4* *2,4 = 0.6*	4.37 dt *3,2 = 4.4* *3,4 = 0.6* *3,P = 0.6*	5.21 t *4,3 = 0.6* *4,2 = 0.6*	H-8: 8.09 s
 **6b** B = 8-azaadenin-9-yl	D_2O [h]	6.42 d *1,2 = 5.8*	5.55 dd *2,1 = 5.8* *2,3 = 4.6*	4.52 dd *3,2 = 4.6* *3,4 = 0.7*	5.31 d *4,3 = 0.7*	H-2: 8.34 s
 **6c** B = 8-azaguanin-9-yl	D_2O [i]	6.20 d *1,2 = 6.1*	5.39 dd *2,1 = 6.1* *2,3 = 4.6*	4.46 dd *3,2 = 4.6* *3,4 = 0.8*	5.27 d *4,3 = 0.8*	–
 **22a** B = 6-*N*-benzoyladenin-9-yl	DMSO [j]	6.87 d *1,2 = 5.7*	6.51 dd *2,1 = 5.7* *2,3 = 5.0*	5.96 dd *3,2 = 5.0* *3,4 = 1.1*	5.70 d *4,3 = 1.1*	H-2: 8.78 s H-8: 8.71 s
 **22b** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [k]	6.71 d *1,2 = 5.7*	6.46 dd *2,1 = 5.7* *2,3 = 5.0*	5.94 dd *3,2 = 5.0* *3,4 = 1.2*	5.68 d *4,3 = 1.2*	H-8: 8.645 s

Table IIa (*continued*)

Compound	Solvent	H-1‘	H-2‘	H-3‘	H-4‘	Base
 **22c** B = 8-azaadenin-9-yl	DMSO [l]	6.245 d *1,2 = 6.4*	5.22 td *2,1 = 6.4* *2,3 = 4.4* *2, OH = 6.7*	4.15 td *3,2 = 4.4* *3,4 = 1.1* *3, OH = 4.5*	5.68 d *4,3 = 1.1*	H-2: 8.33 s NH_2: 8.53 br and 8.18 br
 **22d** B = 8-azaguanin-9-yl	DMSO [m]	6.59 d *1,2 = 4.7*	6.52 t *2,1 = 4.7* *2,3 = 4.8*	5.93 dd *3,2 = 4.7* *3,4 = 2.1*	5.72 d *4,3 = 2.1*	CO−NH: 11.15 bs
 **22e** B = 8-azaguanin-7-yl	DMSO [n]	6,94 d *1,2 = 4.0*	6.56 dd *2,1 = 4.0* *2,3 = 5.1*	5.95 dd *3,2 = 5.1* *3,4 = 2.3*	5.765 d *4,3 = 2.3*	CO−NH: 11.47 bs NH_2: 6.60 br
 **24** B = 8-azaadenin-8-yl	DMSO [o]	6.95 d *1,2 = 4.2*	6.70 q *2,1 = 4.2* *2,3 = 5.1*	6.03 dd *3,2 = 5.1* *3,4 = 2.2*	5.76 d *4,3 = 2.2*	H-2: 8.36 s NH_2: 8.67 br and 8.26 br
 **25** B = 8-azaadenin-7-yl	DMSO [p]	7.14 d *1,2 = 6.4*	6.18 t *2,1 = 6.4* *2,3 = 6.0*	5.73 dd *3,2 = 6.0* *3,4 = 1.3*	6.10 d *4,3 = 1.3*	H-2: 8.295 s NH_2: 8.37 br and 8.15 br
 **26a** B = adenin-9-yl	D_2O [q]	6.52 dd *1,2 = 4.3* *1,F = 14.5*	5.78 dt *2,F = 50.8* *2,1 = 4.3* *2,3 = 4.5*	4.65 ddd *3,2 = 4.5* *3,4 = 1.8* *3,F = 7.0*	5.40 t *4,3 = 1.8* *4,F = 1.8*	H-2: 8.24 s H-8: 8.42 s
 **26b** B = guanin-9-yl	D_2O [r]	6.32 dd *1,2 = 4.5* *1,F = 15.1*	5.77 dt *2,F = 51.0* *2,1 = 4.5* *2,3 = 4.5*	4.66 ddd *3,2 = 4.5* *3,4 = 1.8* *3,F = 6.7*	5.36 t *4,3 = 1.8* *4,F = 1.9*	H-8: 8.05 s
 **26d** B = guanin-9-yl	D_2O [s]	6.04 d *1,2 = 6.7*	5.01 ddd *2,1 = 6.7* *2,3 = 4.5* *2,4 = 0.5*	4.42 dt *3,2 = 4.5* *3,4 = 0.6* *3,P = 0.6*	5.27 t *4,3 = 0.6* *4,2 = 0.5*	H-8: 8.09 s
 **26e** B = 8-azaadenin-9-yl	D_2O [t]	6.43 d *1,2 = 6.2*	5.56 dd *2,1 = 6.2* *2,3 = 4.6*	4.555 dd *3,2 = 6.2* *3,4 = 0.9*	5.395 d *4,3 = 0.9*	H-2: 8.37 s
 **26f** B = 8-azaguanin-9-yl	D_2O [u]	6.235 d *1,2 = 6.6*	5.43 dd *2,1 = 6.6* *2,3 = 4.6*	4.49 bd *3,2 = 4.6* *3,4 < 1.0*	5.34 bs *4,3 < 1.0*	–
 **27a** B = adenin-9-yl Mixture of diastereomers 53:47	DMSO [v] Major	6.39 dd *1,2 = 5.0* *1,F = 14.7*	5.81 dt *2,F = 51.3* *2,1 = 5.0* *2,3 = 4.5*	4.37 qd *3,2 = 4.5* *3,4 = 1.7* *3,F = 5.0* *3, OH = 5.0*	5.16 t *4,3 = 1.7* *4,F = 1.7*	H-2: 8.17 s H-8: 8.25 s
	Minor	6.38 dd *1,2 = 5.0* *1,F = 14.7*	5.78 dt *2,F = 51.3* *2,1 = 5.0* *2,3 = 4.5*	4.355 qd *3,2 = 4.5* *3,4 = 1.7* *3,F = 5.0* *3, OH = 5.0*	5.02 t *4,3 = 1.7* *4,F = 1.7*	H-2: 8.17 s H-8: 8.21 s

(*continued on next page*)

Table IIa (*continued*)

Compound	Solvent	H-1'	H-2'	H-3'	H-4'	Base
 **27b** B = guanin-9-yl Mixture of diastereomers 57:43	DMSO [w]	6.175 dd	5.605 dt	4.27 qd	5.11 t	H-8: 7.79 s
	Major	*1,2 = 5.4*	*2,F = 51.6*	*3,2 = 4.3*	*4,3 = 1.7*	
		1,F = 14.3	*2,1 = 5.4*	*3,4 = 1.7*	*4,F = 1.6*	
			2,3 = 4.3	*3,F = 5.0*		
				3, OH = 5.1		
	minor	6.16 dd	5.58 dt	4.25 qd	4.96 t	H-8: 7.77 s
		1,2 = 5.6	*2,F = 51.7*	*3,2 = 4.3*	*4,3 = 1.6*	
		1,F = 14.2	*2,1 = 5.6*	*3,4 = 1.6*	*4,F = 1.5*	
			2,3 = 4.3	*3,F = 5.0*		
				3, OH = 5.1		

Substituents.

[a] **O–CH_2–P = O($OH)_2$**: 3.81 dd, *J = 12.9, 8.9* Hz and 3.62 dd, *J = 12.9, 9.7* Hz.

[b] **O–CH_2–P = O($OH)_2$**: 3.76 m and 3.53 m.

[c] **3-OBz**: 8.10 m (2x *o*-ArH), 7.62 m (2x *m*-ArH), 7.465 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.97 dd, *J = 13.9; 9.1* Hz and 3.92 dd, *J = 13.9; 9.1* Hz (P–CH_2–O), 4.54 m (2x O–CH<), 1.204 d, *J = 6.2* Hz, 1.207 d, *J = 6.2* Hz, 1.233 d, *J = 6.2* Hz, 1.238 d, *J = 6.2* Hz (2x OiPr); **NHBz**: 11.30 br (NH), 8.05 m (2x *o*-ArH), 7.56 m (2x *m*-ArH), 7.56 m (*p*-ArH).

[d] **NHAc**: 10.82 s (NH), 2.18 s (CH_3); **3-OBz**: 8.07 m (2x *o*-ArH), 7.61 m (2x *m*-ArH), 7.75 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.95 d, *J = 9.5* Hz (P–CH_2–O), 4.57 m (2x O–CH<), 1.121 d, *J = 6.2* Hz, 1.156 d, *J = 6.2* Hz, 1.160 d, *J = 6.2* Hz, 1.186 d, *J = 6.2* Hz (2x OiPr); **O–CO–N($C_6H_5)_2$**: 7.51 m (4x *o*-ArH), 7.45 m (4x *m*-ArH), 7.33 (2x *p*-ArH).

[e] **3-OBz**: 8.05 m (2x *o*-ArH), 7.60 m (2x *m*-ArH), 7.735 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 4.08 dd, *J = 14.0; 9.2* Hz and 4.02 dd, *J = 14.0; 9.4* Hz (P–CH_2–O), 4.64 m (2x O–CH<), 1.234 d, *J = 6.2* Hz, 1.240 d, 6H, *J = 6.2* Hz and 1.254 d, *J = 6.2* Hz (2x OiPr); **NHBz**: 11.29 bs (NH), 8.055 m (2x *o*-ArH), 7.56 m (2x *m*-ArH), 7.65 (*p*-ArH).

[f] **3-OBz**: 8.00 m (2x *o*-ArH), 7.57 m (2x *m*-ArH), 7.72 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 4.05 dd, *J = 13.9; 9.0* Hz and 4.035 dd, *J = 13.9; 9.1* Hz (P–CH_2–O), 4.63 m (2x O–CH<), 1.214 d, *J = 6.2* Hz, 1.225 d, *J = 6.2* Hz, 1.226 d, *J = 6.2* Hz and 1.239 d, *J = 6.2* Hz (2x OiPr); **NHAc**: 10.76 s (NH), 2.23 s (CH_3); **O–CO–N($C_6H_5)_2$**: 7.49 br m (4x *o-ArH*), 7.44 m (4x *m*-ArH), 7.32 (2x *p*-ArH).

[g] **O–CH_2–P = O($OH)_2$**: 3.75 dd, *J = 12.8, 8.6* Hz and 3.50 dd, *J = 12.8, 9.8* Hz.

[h] **O–CH_2–P = O($OH)_2$**: 3.62 dd, *J = 13.4, 8.4* Hz and 3.50 dd, *J = 13.4, 9.5* Hz.

[i] **O–CH_2–P = O($OH)_2$**: 3.67 dd, *J = 13.1, 8.1* Hz and 3.46 dd, *J = 13.1, 9.7* Hz.

[j] **3-OBz**: 7.82 m (2x *o*-ArH), 7.43 m (2x *m*-ArH), 7.625 m (*p*-ArH); **3-OBz**: 8.045 m (2x *o*-ArH), 7.57 m (2x *m*-ArH), 7.72 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.98 m (P–CH_2–O), 4.65 m (2x O–CH<), 1.247 d, *J = 6.2* Hz, 1.255 d, *J = 6.2* Hz, 1.266 d, 6H, *J = 6.4* Hz (2x OiPr); **NHBz**: 11.27 br (NH), 8.055 m (2x *o*-ArH), 7.555 m (2x *m*-ArH), 7.65 m (*p*-ArH).

[k] **2-OBz**: 7.80 m (2x *o*-ArH), 7.41 m (2x *m*-ArH), 7.61 m (*p*-ArH); **3-OBz**: 8.005 m (2x *o*-ArH), 7.56 m (2x *m*-ArH), 7.71 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.97 d, *J = 9.4* Hz (P–CH_2–O), 4.65 m (2x O–CH<), 1.236 d, *J = 6.2* Hz, 1.256 d, *J = 6.2* Hz, 1.263 d, *J = 6.0* Hz and 1.273 d, *J = 6.0* Hz (2x OiPr); **NHAc**: 10.76 s (NH), 2.215 s (CH_3); **O–CO–N($C_6H_5)_2$**: 7.505 m (4x *o*-ArH), 7.44 m (4x *m*-ArH), 7.32 (2x *p*-ArH).

[l] **O–CH_2–P = O($OH)_2$**: 3.69 d, 2H, *J = 8.8* Hz; **2-OH**: 5.66 d, *J = 6.7* Hz; **3-OH**: 5.73 d, *J = 4.5* Hz.

[m] **2-OBz**: 7.97 m (2x *o*-ArH), 7.53 m (2x *m*-ArH), 7.70 m (*p*-ArH); **3-OBz**: 7.85 m (2x *o*-ArH), 7.45 m (2x *m*-ArH), 7.64 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.88 d, 2H, *J = 9.0* Hz (P–CH_2–O), 4.58 m (2x O–CH<), 1.196 d, *J = 6.2* Hz, 1.209 d, *J = 6.2* Hz, 1.222 d, *J = 6.2* Hz and 1.235 d, *J = 6.2* Hz (2x OiPr).

[n] **2-OBz**: 7.94 m (2x *o*-ArH), 7.51 m (2x *m*-ArH), 7.69 m (*p*-ArH); **3-OBz**: 7.87 m (2x *o*-ArH), 7.46 m (2x *m*-ArH), 7.65 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.88 dd, *J = 13.9; 9.4* Hz and 3.80 dd, *J = 13.9; 8.5* Hz, (P–CH_2–O), 4.56 m (2x O–CH<), 1.165 d, *J = 6.2* Hz 1.196 d, *J = 6.2* Hz, 1.202 d, *J = 6.2* Hz and 1.208 d, *J = 6.2* Hz (2x OiPr).

[o] **2-OBz**: 7.86 m (2x *o*-ArH), 7.44 m (2x *m*-ArH), 7.645 m (*p*-ArH); **3-OBz**: 8.00 m (2x *o*-ArH), 7.52 m (2x *m*-ArH), 7.70 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 3.88 dd, *J = 13.9; 9.4* Hz and 3.78 dd, *J = 13.9; 8.6* Hz, (P–CH_2–O), 4.55 m (2x O–CH<), 1.141 d, *J = 6.2* Hz, 1.185 d, *J = 6.2* Hz, 1.187 d, *J = 6.2* Hz and 1.202 d, *J = 6.2* Hz (2x OiPr).

[p] **2-OBz**: 7.24 m (2x *o*-ArH), 7.15 m (2x *m*-ArH), 7.46 m (*p*-ArH); **3-OBz**: 8.00 m (2x *o*-ArH), 7.45 m (2x *m*-ArH), 7.64 m (*p*-ArH); **O–CH_2–P = O($OiPr)_2$**: 4.14 dd, *J = 14.0; 9.0* Hz and 4.12 dd, *J = 14.0; 8.8* Hz, (P–CH_2–O), 4.68 m (2x O–CH<), 1.282 d, *J = 6.2* Hz, 1.285 d, *J = 6.2* Hz and 1.290 d, 6H, *J = 6.2* Hz (2x OiPr).

[q] **O–CH_2–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)($OH)_2$**: 3.99 dd, *J = 13.3; 8.5* Hz and 3.89 dd, *J = 13.2; 10.1* Hz (P–CH_2–O).

[r] **O–CH_2–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)($OH)_2$**: 3.98 dd, *J = 13.3; 8.4* Hz and 3.86 dd, *J = 13.3; 10.3* Hz (P–CH_2–O).

[s] **O–CH_2–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)($OH)_2$**: 3.95 dd, *J = 13.3; 8.2* Hz and 3.82 dd, *J = 13.3; 10.3* Hz (P–CH_2–O).

[t] **O–CH_2–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)($OH)_2$**: 3.775 dd, *J = 13.8; 7.7* Hz and 3.75 dd, *J = 13.8; 9.1* Hz (P–CH_2–O).

[u] **O–CH_2–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)($OH)_2$**: 3.875 dd, *J = 13.6; 7.4* Hz and 3.765 dd, *J = 13.6; 9.9* Hz (P–CH_2–O).

[v] **Major diastereomer: 3-OH**: 6.165 d, *J = 5.0* Hz; **Bu-O-CH($CH_2C_6H_5$)–CO–NH–P(= O)(O–C_6H_5)–CH_2–O**: 0.81 t, 3H, *J = 7.4* Hz, 1.18 m, 2H, 1.39 m, 2H, 3.92 m, 2H (Bu-O-); 4.05 m, 1H, 2.94 m, 1H and 2.735 m, 1H (O–CH–CH_2); 7.38 br, 1H (NH); 7.00–7.30 m, 10H (10x ArH); 3.45 dd, 1H, *J = 13.5; 8.8* Hz and 3.405 dd 1H, *J = 13.5; 8.2* Hz (P–CH_2–O); **minor diastereomer: 3-OH**: 6.155 d, *J = 5.0* Hz; **Bu-O-CH($CH_2C_6H_5$)–CO–NH–P(= O)(O–C_6H_5)–CH_2–O**: 0.785 t, 3H, *J = 7.4* Hz, 1.18 m, 2H, 1.39 m, 2H, 3.90 m, 2H (Bu-O-); 4.07 m, 1H, 2.91 m, 1H and 2.72 m, 1H (O–CH–CH_2); 7.395 br, 1H (NH); 7.00–7.30 m, 10H (10x ArH); 3.84 dd, 1H, *J = 13.7; 8.8* Hz and 3.69 dd 1H, *J = 13.7; 7.0* Hz (P–CH_2–O).

[w] **Major diastereomer: 3-OH**: 6.13 d, *J = 5.1* Hz; **Bu-O-CH($CH_2C_6H_5$)–CO–NH–P(= O)(O–C_6H_5)–CH_2–O**: 0.805 t, 3H, *J = 7.4* Hz, 1.195 m, 2H, 1.41 m, 2H, 3.93 m, 2H (Bu-O-); 4.07 m, 1H, 2.915 ddd, 1H, *J = 13.6; 6.0; 2.0* Hz and 2.72 dd, 1H, *J = 13.6; 8.5* Hz (O–CH–CH_2); 7.38 br, 1H (NH); 7.025–7.275 m, 10H (10x ArH); 3.88 dd, 1H, *J = 13.5; 9.1* Hz and 3.695 dd 1H, *J = 13.5; 7.2* Hz (P–CH_2–O); **minor diastereomer: 3-OH**: 6.12 d, *J = 5.1* Hz; **Bu-O-CH($CH_2C_6H_5$)–CO–NH–P(= O)(O–C_6H_5)–CH_2–O**: 0.805 t, 3H, *J = 7.4* Hz, 1.195 m, 2H, 1.41 m, 2H, 3.905 m, 2H (Bu-O-); 4.07 m, 1H, 2.96 ddd, 1H, *J = 13.5; 6.2; 1.5* Hz and 2.75 dd, 1H, *J = 13.5; 9.1* Hz (O–CH–CH_2); 7.395 br, 1H (NH); 7.025–7.275 m, 10H (10x ArH); 3.46 dd, 1H, *J = 13.5; 8.3* Hz and 3.43 dd, 1H, *J = 13.5; 8.9* Hz (P–CH_2–O).

[x] Coupling constants are written in italics in a shortened form (e.g. instead *J(1',2') = 4.3* Hz we type simply *1,2 = 4.3*).

for $C_{27}H_{33}O_{11}NaP$ calculated: 587.16527; measured: 587.16534; IR (CHCl3, cm^{-1}): 2981, 2878, 1734, 1602, 1492, 1467, 1452, 1386, 1375, 1364, 1281, 1263, 1224, 1179, 1163, 1123, 1071, 1024, 991, 981, 888, 711. For NMR data, see table Ia and Ib.

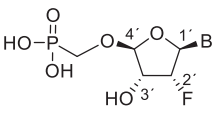
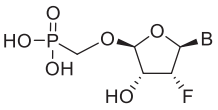
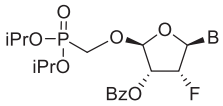
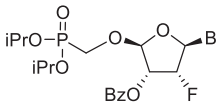
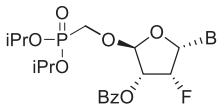
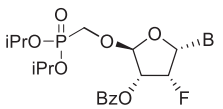
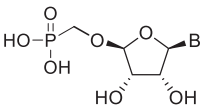
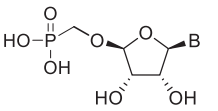
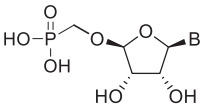
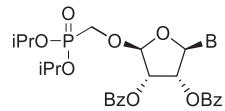
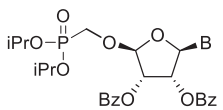
*4.19. (2R,3R,4S,5R)-2-(6-benzamido-9H-purin-9-yl)-4-benzoyl-5-((diisopropoxyphosphoryl)methoxy)tetrahydrofuran-3-yl benzoate (**22a**)*

Bis(trimethylsilyl)acetamide (1.1 mL; 4.5 mmol) was added to 6*N*-benzoyladenine (335 mg; 1.4 mmol) in 1,2-dichloroethane (14 mL), and the reaction mixture was stirred for 1 h at 60 °C. The mixture was concentrated and co-evaporated with dry toluene (2 × 20 mL). Next, acetate **21** (565 mg; 1 mmol) in ACN (10 mL) was added, followed by $SnCl_4$ (600 μL; 5.1 mmol). The mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 1 mL of pyridine, filtered and concentrated. Product **22a** was isolated by chromatography on a silica gel (0–5% methanol in chloroform) in a yield of 160 mg (50%). HRMS $(M + Na)^+$ for $C_{37}H_{38}O_{10}N_5NaP$ calculated: 766.22485; measured: 766.22449; IR (coating, cm-1): 3227, 3090, 3065, 3032, 2978, 2925, 2870, 2854, 1733, 1700, 1610, 1602, 1583, 1512, 1490, 1452, 1386, 1376, 1334, 1316, 1269, 1252, 1178, 1158, 1126, 1105, 1063, 1024, 990, 937, 889, 711, 672, 642, 528. For NMR data, see table IIa and IIb.

*4.20. (2R,3R,4S,5R)-2-(2-acetamido-6-((diphenylcarbamoyl)oxy)-9H-purin-9-yl)-5-((diisopropoxyphosphoryl)methoxy) tetrahydrofuran-3,4-diyl dibenzoate (**22b**)*

Bis(trimethylsilyl)acetamide (1.1 mL; 4.5 mmol) was added to *N*2-acetyl-O6-(diphenylcarbamoyl)guanine (550 mg; 1.4 mmol) in

Table IIb
^{13}C and ^{31}P NMR data of compounds **5, 6, 16** and **22**–**27** [x]

Compound	Solvent	C-1'	C-2'	C-3'	C-4'	Base	^{31}P	^{19}F
 **5a** B = Adenin-9-yl	D_2O [a]	88.14 *1,F = 34.0*	96.60 *2,F = 192.0*	75.51 *3,F = 15.1*	112.10 *4,P = 12.1* *4,F = 3.2*	C-2: 155.51 C-4: 151.41 C-5: 121.14 C-6: 158.18 C-8: 142.68	14.93	−210.06
 **5b** B = Guanin-9-yl	D_2O [b]	87.78	96.18	75.27	111.87	C-2: n.d. C-4: 154.37 C-5: 118.81 C-6: n.d. C-8: 140.52	14.15	−209.59
 **16a** B = 6-*N*-benzoyladenin-9-yl	DMSO [c]	86.31 *1,F = 34.4*	91.24 *2,F = 193.1*	74.45 *3,F = 14.0*	106.69 *4,P = 12.4* *4,F = 1.1*	C-2: 152.62 C-4: 152.14 C-5: 125.77 C-6: 150.94 C-8: 143.32	18.29	−204.85
 **16b** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [d]	86.57 *1,F = 15.0*	91.14 *2,F = 192.6*	74.33 *3,F = 13.9*	106.95 *4,P = 13.2*	C-2: 150.19 C-4: 154.35 C-5: 120.32 C-6: 152.57 C-8: 144.37	18.93	−203.23
 **16c** B = 6-N-benzoyladenin-9-yl	DMSO [e]	82.10 *1,F = 15.6*	88.90 *2,F = 197.1*	74.78 *3,F = 14.0*	105.04 *4,P = 11.7*	C-2: 152.33 C-4: 152.13 C-5: 124.96 C-6: 150.75 C-8: 142.98 *8,F = 5.5*	19.18	−207.71
 **16d** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [f]	82.59 *1,F = 15.7*	88.63 *2,F = 197.5*	74.61 *3,F = 16.1*	105.42 *4,P = 12.2*	C-2: 150.19 C-4: 154.55 C-5: 119.67 C-6: 152.75 C-8: 144.05 *8,F = 5.1*	19.09	−206.65
 **6a** B = guanin-9-yl	D_2O [g]	89.27	77.15	76.56	111.95 *4,P = 11.8*	C-2: 156.79 C-4: 154.74 C-5: 118.76 C-6: 161.68 C-8: 140.52	14.35	–
 **6b** B = 8-azaadenin-9-yl	D_2O [h]	91.41	75.65	76.69	112.28 *4,P = 11.0*	C-2: 159.86 C-4: 152.00 C-5: 127.19 C-6: 158.94	15.93	–
 **6c** B = 8-azaguanin-9-yl	D_2O [i]	91.09	76.23	76.57	112.17 *4,P = 10.9*	C-2: 158.82 C-4: 155.02 C-5: 127.40 C-6: 160.97	15.38	–
 **22a** B = 6-*N*-benzoyladenin-9-yl	DMSO [j]	85.82	74.08	74.44	106.20 *4,P = 12.4*	C-2: 152.16 C-4: 152.38 C-5: 125.72 C-6: 150.80 C-8: 149.09	19.16	–
 **22b** B = 2-*N*-acetyl-6-*O*-diphenyl carbamoylguanin-9-yl	DMSO [k]	86.12	73.82	74.43	106.34 *4,P = 13.4*	C-2: 150.23 C-4: 154.72 C-5: 120.36 C-6: 152.70 C-8: 144.24	19.42	–

(*continued on next page*)

Table IIb (*continued*)

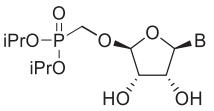
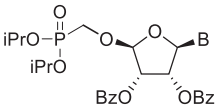
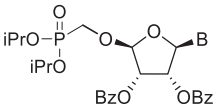
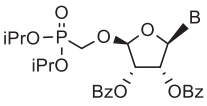
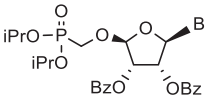
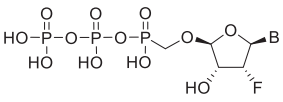
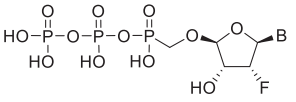
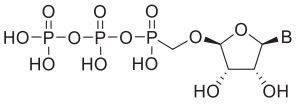
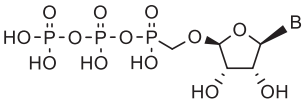
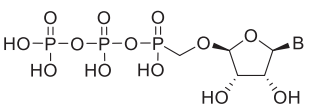
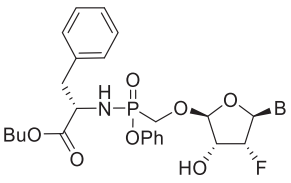
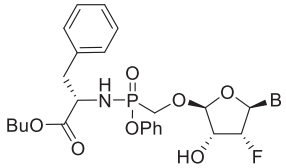
Compound	Solvent	C-1‘	C-2‘	C-3‘	C-4‘	Base	^{31}P	^{19}F
 **22c** B = 8-azaadenin-9-yl	DMSO [l]	88.35	72.46	73.92	108.70 *4,P = 11.8*	C-2: 157.39 C-4: 149.95 C-5: 124.14 C-6: 156.38	19.77	–
 **22d** B = 8-azaguanin-9-yl	DMSO[m]	86.13	73.22	74.63	106.54 *4,P = 12.9*	C-2: 155.69 C-4: 152.30 C-5: 124.66 C-6: 156.25	19.06	–
 **22e** B = 8-azaguanin-7-yl	DMSO [n]	89.10	73.65	74.75	107.15 *4,P = 12.4*	C-2: 154.29 C-4: 153.72 C-5: 113.66 C-6: 161.55	18.70	–
 **24** B = 8-azaadenin-8-yl	DMSO [o]	86.94	73.36	74.41	106.97 *4,P = 12.5*	C-2: 157.61 C-4: 149.56 C-5: 124.12 C-6: 156.46	18.20	–
 **25** B = 8-azaadenin-7-yl	DMSO [p]	91.99	70.82	72.63	107.40 *4,P = 11.7*	C-2: 157.80 C-4: 157.12 C-5: 126.12 C-6: 158.00	n.d.	–
 **26a** B = adenin-9-yl	D_2O [q]	88.24 *1,F = 34.1*	96.51 *2,F = 192.3*	75.42 *3,F = 14.9*	112.14 *4,P = 12.2* *4,F = 3.2*	C-2: 155.49 C-4: 151.68 C-5: 121.36 C-6: 158.30 C-8: 142.89	P_α: 8.39 *α,β = 25.6* P_β: 22.10 *β,α = 25.6* *β,γ = 19.7* P_γ: 9.48 *γ,β = 19.7*	–210.72
 **26b** B = guanin-9-yl	D_2O [r]	87.85 *1,F = 33.9*	95.38 *2,F = 191.8*	75.11 *3,F = 14.9*	111.72 *4,P = 12.0* *4,F = 3.2*	C-2: 156.71 C-4: 154.34 C-5: 118.85 C-6: 161.67 C-8: 140.50	P_α: 8.62 *α,β = 25.7* P_β: 22.02 *β,α = 25.7* *β,γ = 16.7* P_γ: 9.60 *γ,β = 16.7*	–210.89
 **26d** B = guanin-9-yl	D_2O [s]	89.36	76.78	76.41	111.82 *4,P = 12.0*	C-2: 156.79 C-4: 154.81 C-5: 118.84 C-6: 161.75 C-8: 140.59	P_α: 8.36 *α,β = 25.8* P_β: 22.51 *β,α = 25.8* *β,γ = 19.6* P_γ: 9.82 *γ,β = 19.6*	–
 **26e** B = 8-azaadenin-9-yl	D_2O [t]	91.38	75.54	76.52	112.34 *4,P = 9.8*	C-2: 159.95 C-4: 152.13 C-5: 127.33 C-6: 159.08	P_α: 9.06 *α,β = 26.2* P_β: 22.03 *β,α = 26.2* *β,γ = 19.4* P_γ: 9.27 *γ,β = 19.4*	–
 **26f** B = 8-azaguanin-9-yl	D_2O [u]	91.34	74.71	76.23	111.88 *4,P = 10.5*	C-2: 160.82 C-4: 154.82 C-5: 127.39 C-6: 158.54	P_α: 9.21 *α,β = 26.2* P_β: 22.30 *β,α = 26.2* *β,γ = 19.4* P_γ: 9.84 *γ,β = 19.4*	–
 **27a** B = adenin-9-yl Mixture of diastereomers 53:47	DMSO [v] Major	84.73 *1,F = 33.0*	93.16 *2,F = 191.1*	72.35 *3,F = 15.0*	108.30 *4,P = 10.8* *4,F = 4.1*	C-2: 153.24 C-4: 149.67 C-5: 118.93 C-6: 156.33 C-8: 139.06	23.18	–211.17
	Minor	84.63 *1,F = 33.2*	93.30 *2,F = 191.2*	72.30 *3,F = 15.0*	108.38 *4,P = 11.8* *4,F = 3.2*	C-2: 153.24 C-4: 149.68 C-5: 118.88 C-6: 156.33 C-8: 139.03	22.74	–211.28

Table IIb (*continued*)

Compound	Solvent	C-1‘	C-2‘	C-3‘	C-4‘	Base	^{31}P	^{19}F
 **27b** B = guanin-9-yl Mixture of diastereomers 57:43	DMSO[w]	84.14	93.37	72.22	108.00	C-2: 154.22	23.29	−212.34
	Major	*1,F = 32.5*	*2,F = 191.7*	*3,F = 15.0*	*4,P = 4.2*	C-4: 151.52 C-5: 116.69 C-6: 156.85 C-8: 135.00		
	minor	84.11	93.20	72.16	108.08	C-2: 154.19	22.95	−212.81
		1,F = 32.5	*2,F = 191.6*	*3,F = 15.0*	*4,P = 4.2*	C-4: 151.48 C-5: 116.78 C-6: 156.88 C-8: 135.23		

Substituents.

[a] **O–CH$_2$–P = O(OH)$_2$**: 68.13 d, *J = 155.*9 Hz.

[b] **O–CH$_2$–P = O(OH)$_2$**: 68.59.

[c] **O–CH$_2$–P = O(OiPr)$_2$**: 62.62 d, *J = 166.*0 Hz (P–CH$_2$–O), 71.02 d, *J = 6.*3 Hz (2x O–CH<), 23.97 d, *J = 3.*5 Hz, 23.99 d, *J = 3.*5 Hz, 24.04 d, *J = 4.*4 Hz, 24.12 d, *J = 3.*8 Hz (2x OiPr); 3-**OBz**: 164.78 (C=O), 128.50 (*i*-ArC), 129.86 (2x *o*-ArC), 129.32 (2x *m*-ArC), 134.52 (*p*-ArC); **NHBz:** 165.98 (C=O), 133.55 (i-ArC), 128.78 (2x *o*-ArC and 2x *m*-ArC), 132.82 (*p*-ArC).

[d] **NHAc**: 168.71 (C=O), 24.71 (CH$_3$); 3-**OBz**: 164.45 (C=O), 128.53 (*i*-ArC), 129.70 (2x *o*-ArC), 129.22 (2x *m*-ArC), 134.35 (*p*-ArC); **O–CH$_2$–P = O(OiPr)$_2$**: 62.24 d, *J = 166.*3 Hz (P–CH$_2$–O), 70.85 d, *J = 6.*3 Hz (2x O–CH<), 23.69 d, *J =* 6.3 Hz, 23.72 d, *J = 4.*4 Hz, 23.86 d, *J = 4.*0 Hz, 23.89 d, *J = 4.*0 Hz (2x OiPr); **O–CO–N(C$_6$H$_5$)$_2$**: 155.54 (C=O), 141.75 (2x *i-ArC*), 126.67 (4x *o*-ArC), 129.61 (4x *m*-ArC), 127.10 (2x *p*-ArC).

[e] **O–CH$_2$–P = O(OiPr)$_2$**: 62.31 d, *J = 165.*8 Hz (P–CH$_2$–O), 70.80 d, *J = 6.*2 Hz and 70.81 d, *J = 6.*2 Hz (2x O–CH<), 23.84 d, *J = 4.*6 Hz, 23.85 d, *J = 4.*4 Hz and 23.98 d, 2C, *J = 3.*8 Hz (2x OiPr); 3-**OBz**: 164.64 (C=O), 128.42 (*i*-ArC), 129.72 (2x *o*-ArC), 129.23 (2x *m*-ArC), 134.40 (*p*-ArC); **6-NHBz**: 165.85 (C=O), 133.45 (*i*-ArC), 128.71 (2x *o*-ArC), 128.68 (2x *m*-ArC), 132.72 (*p*-ArC).

[f] **O–CH$_2$–P = O(OiPr)$_2$**: 62.47 d, *J = 166.*0 Hz (P–CH$_2$–O), 70.77 d, *J = 5.*9 Hz (2x O–CH<), 23.79 d, *J = 4.*5 Hz, 23.81 d, *J =* 4.5 Hz and 23.95 d, 2C, *J = 3.*7 Hz (2x OiPr); 3-**OBz**: 164.62 (C=O), 128.40 (*i-ArC*), 129.67 (2x *o*-ArC), 129.17 (2x *m*-ArC), 134.34 (*p*-ArC); **NHAc:** 169.19 (C=O), 24.86 (CH$_3$); **O–CO–N(C$_6$H$_5$)$_2$**: 155.45 (C=O), 141.71 (2x *i*-ArC), 127.17 (4x *o*-ArC), 129.60 (4x *m*-ArC), 127.53 (2x *p*-ArC).

[g] **O–CH$_2$–P = O(OH)$_2$**: 67.95 d, *J = 154.*5 Hz.

[h] **O–CH$_2$–P = O(OH)$_2$**: 66.72 d, *J = 156.*7 Hz.

[i] **O–CH$_2$–P = O(OH)$_2$**: 67.37 d, *J = 154.*8 Hz.

[j] **O–CH$_2$–P = O(OiPr)$_2$**: 62.09 d, *J = 166.*3 Hz (P–CH$_2$–O), 70.91 d, *J = 6.*3 Hz and 70.92 d, *J = 6.*3 Hz (2x O–CH<), 23.82 d, 2C, *J = 4.*6 Hz, 23.94 d, *J = 4.*1 Hz and 23.97 d, *J = 4.*1 Hz (2x OiPr); **2-OBz**: 164.63 (C=O), 128.31 (*i*-ArC), 129.49 (2x *o*-ArC), 128.95 (2x *m*-ArC), 134.20 (*p*-ArC); 3-**OBz**: 164.66 (C=O), 128.53 (*i*-ArC), 129.67 (2x *o*-ArC), 129.16 (2x *m-ArC*), 134.34 (*p*-ArC); **NHBz:** 165.82 (C=O), 133.50 (*i*-ArC), 128.69 (2x *o*-ArC), 128.66 (2x *m*-ArC), 132.67 (*p*-ArC).

[k] **O–CH$_2$–P = O(OiPr)$_2$**: 61.97 d, *J = 167.*1 Hz (P–CH$_2$–O), 70.99 d, *J = 6.*3 Hz and 71.09 d, *J = 6.*3 Hz (2x O–CH<), 23.79 d, *J = 4.*4 Hz, 23.81 d, *J = 4.*4 Hz and 23.94 d, 2C, *J = 3.*6 Hz (2x OiPr); **2-OBz**: 164.63 (C=O), 128.32 (*i*-ArC), 129.53 (2x *o*-ArC), 128.93 (2x *m*-ArC), 134.20 (*p-ArC*); 3-**OBz**: 164.61 (C=O), 128.56 (*i-ArC*), 129.60 (2x *o-ArC*), 129.18 (2x *m*-ArC), 134.36 (*p*-ArC); **NHAc:** 169.06 (C=O), 24.76 (CH$_3$); **O–CO–N(C$_6$H$_5$)$_2$**: 155.53 (C=O), 141.76 (2x *i*-ArC), 127.12 (4x *o*-ArC), 129.60 (4x *m*-ArC), 127.54 (2x *p*-ArC).

[l] **O–CH$_2$–P = O(OiPr)$_2$**: 61.20 d, *J = 165.*2 Hz (P–CH$_2$–O), 70.50 d, *J = 6.*2 Hz and 70.65 d, *J = 6.*2 Hz (2x O–CH<), 23.81 d, *J = 4.*7 Hz, 23.82 d, *J = 4.*5 Hz, 23.96 d, *J = 3.*7 Hz and 24.00 d, *J = 3.*7 Hz (2x OiPr).

[m] **O–CH$_2$–P = O(OiPr)$_2$**: 61.94 d, *J = 164.*2 Hz (P–CH$_2$–O), 70.87 d, *J = 6.*2 Hz and 70.92 d, *J = 6.*2 Hz (2x O–CH<), 23.75 d, *J = 4.*7 Hz, 23.78 d, *J = 4.*6 Hz, 23.93 d, *J = 3.*8 Hz and 23.94 d, *J = 3.*9 Hz (2x OiPr); **2-OBz**: 164.69 (C=O), 128.49 (*i*-ArC), 129.61 (2x *o*-ArC), 129.14 (2x *m*-ArC), 134.34 (*p*-ArC); 3-**OBz**: 164.66 (C=O), 128.33 (*i*-ArC), 129.56 (2x *o*-ArC), 129.03 (2x *m*-ArC), 134.27 (*p*-ArC).

[n] **O–CH$_2$–P = O(OiPr)$_2$**: 62.22 d, *J = 165.*0 Hz (P–CH$_2$–O), 70.77 d, *J = 6.*2 Hz and 70.88 d, *J = 6.*2 Hz (2x O–CH<), 23.73 d, *J = 4.*5 Hz, 23.76 d, *J =* 4.5 Hz, 23.91 d, *J = 3.*5 Hz and 23.93 d, *J = 3.*5 Hz (2x OiPr); **2-OBz**: 164.67 (C=O), 128.46 (*i*-ArC), 129.56 (2x *o*-ArC), 129.13 (2x *m*-ArC), 134.33 (*p*-ArC); 3-**OBz**: 164.62 (C=O), 128.34 (*i*-ArC), 129.59 (2x *o*-ArC), 129.02 (2x *m*-ArC), 134.27 (*p*-ArC).

[o] **O–CH$_2$–P = O(OiPr)$_2$**: 62.13 d, *J = 165.*7 Hz (P–CH$_2$–O), 70.70 d, *J = 6.*2 Hz and 70.83 d, *J = 6.*2 Hz (2x O–CH<), 23.69 d, *J = 4.*7 Hz, 23.74 d, *J = 4.*6 Hz, 23.89 d, *J = 3.*8 Hz and 23.92 d, *J = 3.*8 Hz (2x OiPr); **2-OBz**: 164.67 (C=O), 128.37 (i-ArC), 129.59 (2x *o*-ArC), 128.97 (2x *m*-ArC), 134.22 (*p*-ArC); **3-OBz**: 164.72 (C=O), 128.48 (*i-ArC*), 129.68 (2x *o*-ArC), 129.10 (2x *m*-ArC), 134.31 (*p*-ArC).

[p] **O–CH$_2$–P = O(OiPr)$_2$**: 62.14 d, *J = 166.*0 Hz (P–CH$_2$–O), 71.04 d, *J = 6.*3 Hz and 71.06 d, *J = 6.*3 Hz (2x O–CH<), 23.96 d, 2C, *J = 4.*4 Hz, 24.07 d, *J = 3.*6 Hz and 24.08 d, *J = 3.*8 Hz (2x OiPr); **2-OBz**: 163.83 (C=O), 127.81 (*i*-ArC), 129.03 (2x *o*-ArC), 128.74 (2x *m*-ArC), 134.22 (*p*-ArC); **3-OBz**: 164.81 (C=O), 128.47 (*i*-ArC), 129.94 (2x *o*-ArC), 128.99 (2x *m*-ArC), 134.22 (*p-ArC*).

[q] **O–CH$_2$–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)(OH)$_2$**: 67.24 d, *J = 164.*5 Hz (P–CH$_2$–O).

[r] **O–CH$_2$–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)(OH)$_2$**: 66.96 d, *J = 164.*9 Hz (P–CH$_2$–O).

[s] **O–CH$_2$–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)(OH)$_2$**: 66.54 d, *J = 164.*8 Hz (P–CH$_2$–O); ’

[t] **O–CH$_2$–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)(OH)$_2$**: 66.39 d, *J = 163.*7 Hz (P–CH$_2$–O).

[u] **O–CH$_2$–P(= O)(OH)–O–P(= O)(OH)–O–P(= O)(OH)$_2$**: 66.18 d, *J = 164.*2 Hz (P–CH$_2$–O).

[v] **Major diastereomer: Bu-O-CH(CH$_2$C$_6$H$_5$)–CO–NH–P(= O)(O–C$_6$H$_5$)–CH$_2$–O**: 13.73, 18.62, 30.16, 64.49 (Bu-O-); 55.41, 39.74 (O–CH–CH$_2$); 150.30 and 137.10 (2x *i*-ArC), 120.7–129.7 (10x ArC); 172.49 (C=O), 63.34 d, *J = 156.*5 Hz (P–CH$_2$–O); **minor diastereomer: Bu-O-CH(CH$_2$C$_6$H$_5$)–CO–NH–P(= O)(O–C$_6$H$_5$)–CH$_2$–O**: 13.68, 18.62, 30.19, 64.37 (Bu-O-); 55.35, 39.46 (O–CH–CH$_2$); 150.25 and 137.19 (2x *i*-ArC), 120.7–129.7 (10x ArC); 172.71 (C=O), 63.07 d, *J = 154.*7 Hz (P–CH$_2$–O).

[w] **Major diastereomer: Bu-O-CH(CH$_2$C$_6$H$_5$)–CO–NH–P(= O)(O–C$_6$H$_5$)–CH$_2$–O**: 13.66, 18.61, 30.15, 64.48 (Bu-O-); 55.37, 39.46 (O–CH–CH$_2$); 137.06 (*i*-ArC), 129.41 (2x *o*-ArC), 128.37 (2x *m*-ArC), 124.56 (*p*-ArC) (C$_6$H$_5$), 172.68 d, *J = 2.*6 Hz (C=O), 150.20 d, *J = 9.*2 Hz (*i-ArC*), 120.68 d, *J = 4.*5 Hz (2x *o*-ArC), 129.65 (2x *m*-ArC), 126.67 (*p*-ArCH) (C$_6$H$_5$); 62.96 d, *J = 154.*9 Hz (P–CH$_2$–O); **minor diastereomer: Bu-O-CH(CH$_2$C$_6$H$_5$)–CO–NH–P(= O)(O–C$_6$H$_5$)–CH$_2$–O**: 13.70, 18.60, 30.17, 64.36 (Bu-O-); 55.33, 39.70 (O–CH–CH$_2$); 137.18 (*i*-ArC), 129.52 (2x *o*-ArC), 128.29 (2x *m*-ArC), 124.62 (*p*-ArC) (C$_6$H$_5$), 172.48 d, *J = 2.*5 Hz (C=O), 150.27 d, *J = 9.*2 Hz (*i*-ArC), 120.74 d, *J = 4.*5 Hz (2x *o*-ArC), 129.63 (2x *m*-ArC), 126.71 (p-ArC) (C$_6$H$_5$); 63.25 d, *J = 157.*6 Hz (P–CH$_2$–O).

[x] Coupling constants are written in italics in a shortened form (e.g. instead *J(C1‘,F) = 34.*0 Hz we type simply *1,F = 34.0*).

1,2-dichloroethane (14 mL), and the reaction mixture was stirred for 1 h at 60 °C. The mixture was concentrated and co-evaporated with dry toluene (3 × 20 mL). Then, the acetate **21** (565 mg; 1 mmol) in ACN (10 mL) was added, followed by $SnCl_4$ (600 μL; 5.1 mmol). The mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 1 mL of pyridine, filtered and concentrated. Product **22b** was isolated by chromatography on a silica gel (0–100% EtOAc in toluene) in a yield of 340 mg (42%). HRMS $(M + Na)^+$ for $C_{45}H_{45}O_{12}N_6NaP$ calculated: 915.27253; measured: 915.27259; IR ($CHCl_3$, cm^{-1}): 3318, 3185, 1737, 1699, 1618, 1598, 1591, 1519, 1511, 1492, 1452, 1386, 1374, 1315, 1298, 1273, 1219, 1180, 1168, 1123, 1106, 1023, 989, 907, 887, 805, 728, 719, 713, 641, 531. For NMR data, see table IIa and IIb.

*4.21. Diisopropyl ((((2R,3S,4R,5R)-5-(7-amino-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy) methyl)phosphonate (**22c**)*

$SnCl_4$ (2.6 mL; 22 mmol) was added dropwise to the heterogenic mixture of the acetate **21** (4.15 g; 7.35 mmol) and 8-azaadenine (1 g; 7.35 mmol) in dry acetonitrile (30 mL). The mixture was warmed to 60 °C and stirred for 3 h. The reaction was then quenched by the addition of pyridine (3 mL), filtered and adsorbed on a silica gel. The product of nucleosidation was isolated by chromatography on a silica gel (0–6% methanol in chloroform) as a mixture of **23** and **25** regioisomers (in ratio 1:3 according NMR) in a yield of 3.06 g (65%) as faster eluting derivatives followed by compound **24** in a yield of 850 mg (18%) as a slower eluting regioisomer. The mixture of regioisomers **23** and **25** was then stirred in sat. NH_3 in 50% aq. MeOH (30 mL) for 16 h at room temperature, concentrated, dissolved in 80% aq. AcOH (20 mL) and stirred for 1 day at room temperature. The 8-azaadenine-7-yl derivative de-purinated, and product **22c** was isolated by chromatography on a silica gel (0–12% methanol in chloroform) in a yield of 500 mg (16%). HRMS $(M + Na)^+$ for $C_{15}H_{25}O_7N_6NaP$ calculated: 455.14145; measured: 455.14099; IR: 3449, 2980, 1700, 1652, 1574, 1466, 1409, 1376, 1335, 1264, 1226, 1178, 1139, 1106, 1081, 1040, 992, 926, 889. For NMR data, see table IIa and IIb.

*4.22. (2R,3R,4S,5R)-2-(5-amino-7-hydroxy-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl)-5-((diisopropoxyphosphoryl)methoxy) tetrahydrofuran-3,4-diyl dibenzoate (**22d**)*

Bis(trimethylsilyl)acetamide (3 mL; 12 mmol) was added to 8-azaguanine (400 mg; 2.6 mmol) in 1,2-dichloroethane (18 mL), and the reaction mixture was stirred for 1 h at 60 °C. The mixture was concentrated, co-distilled with dry toluene (2 × 20 mL), and then added to the acetate **21** (1.52 g; 2.7 mmol) in ACN (20 mL). Finally, $SnCl_4$ (2 mL; 17 mmol) was added in one portion, and the mixture was stirred for 2 h at room temperature. The reaction was then quenched by the addition of 2 mL of pyridine, filtered and concentrated. The reaction afforded a mixture of compounds **22d** and **22e** in a 1:5 ratio. Product **22d** was isolated by chromatography on a silica gel (0–5% methanol in DCM) in a yield of 160 mg (10%) as a faster eluting regioisomer. HRMS $(M + Na)^+$ for $C_{29}H_{33}O_{10}N_6NaP$ calculated: 679.18880; measured: 679.18901; IR ($CHCl_3$, cm-1): 3319, 3165, 2980, 2875, 1733, 1706, 1643, 1601, 1493, 1466, 1452, 1386, 1376, 1316, 1274, 1243, 1179, 1121, 1106, 1026, 996, 891, 774, 712, 685. For NMR data, see table IIa and IIb.

*4.23. (2R,3R,4S,5R)-2-(5-amino-7-hydroxy-1H-[1,2,3]triazolo[4,5-d]pyrimidin-1-yl)-5-((diisopropoxyphosphoryl)methoxy) tetrahydrofuran-3,4-diyl dibenzoate (**22e**)*

Nucleoside phosphonate **22e** was prepared as an undesired product of the preparation of nucleoside phosphonate **22d**. Product **22e** was isolated by chromatography on a silica gel (0–5% methanol in DCM) in a yield of 830 mg (50%) as a slower regioisomer. For NMR data, see table IIa and IIb.

*4.24. ((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic acid (**1**)*

Bromotrimethylsilane (490 μL; 3.7 mmol) was added to **22a** (275 mg; 0.37 mmol) in pyridine (5 mL), and the mixture was stirred for 6 h and concentrated. The residue was diluted with saturated NH3 in 50% MeOH/H_2O (20 mL), stirred for 16 h at room temperature and then concentrated. Nucleotide **1** was isolated by reverse phase chromatography (first 15 min of isocratic elution with 0.1 M TEAB, then 35 min gradient 0–15% MeOH in 0.1 M TEAB) in a yield of 134 mg (80%).

Spectral data were in accordance with literature values [5].

*4.25. ((((2R,3S,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic acid (**6a**)*

Bromotrimethylsilane (490 μL; 3.7 mmol) was added to **22b** (330 mg; 0.37 mmol) in pyridine (5 mL), the mixture was stirred for 6 h, and then concentrated. The residue was diluted with saturated NH_3 in 50% MeOH/H_2O (20 mL), stirred for 16 h at room temperature and concentrated. Nucleotide **6a** was isolated by reverse phase chromatography (first 15 min of isocratic elution with 0.1 M TEAB, then 35 min gradient 0–15% MeOH in 0.1 M TEAB) in a yield of 138 mg (80%). HRMS $(M - H)^-$ for $C_{10}H_{13}O_8N_5P$ calculated: 362.05072; measured: 362.05020; IR (CHCl3, cm^{-1}): 3402, 3153, 2823, 2739, 2680, 2492, 1693, 1645, 1605, 1571, 1480, 1451, 1398, 1229, 1162, 1093, 1038, 999, 965, 783, 682, 574. For NMR data, see table IIa and IIb.

*4.26. ((((2R,3S,4R,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl) phosphonic acid (**6b**)*

Bromotrimethylsilane (1.6 mL; 11.6 mmol) was added to **22c** (500 mg; 1.16 mmol) in pyridine (20 mL). The mixture was stirred for 6 h and concentrated. Nucleotide **6b** was isolated by reverse phase chromatography (first 15 min of isocratic elution with 0.1 M TEAB, then 35 min gradient 0–15% MeOH in 0.1 M TEAB) in a yield of 980 mg (84%). HRMS $(M - H)^-$ for $C_9H_{12}O_7N_6P$ calculated: 347.05106; measured: 347.05098; IR (coating MeOH, cm^{-1}): 3395, 3325, 3165, 2738, 2677, 2571, 2491, 2349, 1660, 1607, 1577, 1468, 1266, 1140, 1061, 1061, 1061, 913, 849, 799, 684, 645. For NMR data, see table IIa and IIb.

*4.27. ((((2R,3S,4R,5R)-5-(5-amino-7-hydroxy-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy) methyl)phosphonic acid (**6c**)*

Bromotrimethylsilane (330 μL; 2.5 mmol) was added to **22d** (160 mg; 0.24 mmol) in pyridine (5 mL), the mixture was stirred for 6 h, and then concentrated. The residue was diluted with saturated NH_3 in 50% MeOH/H_2O (10 mL), stirred for 16 h at room temperature, and then concentrated. Nucleotide **6c** was isolated by reverse phase chromatography (first 15 min of isocratic elution with 0.1 M TEAB, then 35 min gradient 0–15% ACN in 0.1 M TEAB) in a yield of 100 mg (90%). HRMS $(M - H)^-$ for $C_9H_{12}O_8N_6P$ calculated: 363.04597; measured: 363.04563; IR ($CHCl_3$, cm^{-1}): 3419, 3167, 2686, 2491, 1711, 1639, 1532, 1457, 1240, 1112, 1056, 1039, 788, 682; NMR: For NMR data, see table IIa and IIb.

*4.28. ((((2R,3R,4R,5R)-5-(6-amino-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic diphosphoric anhydride (**26a**)*

Triethylammonium salt of phosphonate **5a** (90 mg; 0.2 mmol) was converted to tetrabutylammonium salt (Dowex® 50WX 8 in tetrabutylammonium cycle) and dried by co-evaporation with anhydrous pyridine. The mixture of phosphonate salt, imidazole (211 mg; 3.1 mmol), and tri-*N*-octylamine (0.57 mL; 1.3 mmol) was dried by co-evaporation with anhydrous DMF (2 × 10 mL). The semi-solid residue was dissolved in anhydrous DMF (12 mL), triphenylphosphine (341 mg; 1.3 mmol), and 2,2′-dipyridyldisulfide (Aldrithiol™, 286 mg; 1.3 mmol) were added, and the mixture was

stirred for 16 h at room temperature.

The reaction mixture was added dropwise to the precipitation solution: sodium perchlorate monohydrate (702 mg; 5 mmol) and triethylamine (4 mL) in peroxide free mixture of acetone (60 mL) and diethylether (36 mL) at 0 °C. The solution was allowed to precipitate at 0 °C for about 30 min. The precipitate was then separated by centrifugation (10000 RPM, 3 °C, 20 min), washed with the precipitation solution, and then with the dry diethylether. Solid imidazolide was dried in vacuo. Tributylammonium pyrophosphate (0.5 M solution in DMSO, 1.2 mL; 0.6 mmol) was added to imidazolide, and the solution was kept at room temperature for 48 h. The phosphonodiphosphate was purified by column chromatography on reverse phase (Phenomenex Luna C18 5 μm), using a linear gradient of acetonitrile (0–5%) in triethylamine bicarbonate buffer (0.1 M).

Triethylammonium salt of the product was converted to sodium salt using Dowex® 50WX 8, Na^+ cycle yielding 93 mg (65%) of desired triphosphate analogue **26a**. HRMS $(M - H)^-$ for $C_{10}H_{14}O_{12}N_5FP_3$ calculated: 507.98413; measured: 507.98370; IR (KBr, cm^{-1}): 3428, 1695, 1647, 1579, 1479, 1424, 1332, 1247, 1077, 1042, 899, 842, 719. For NMR data, see table IIa and IIb.

*4.29. ((((2R,3R,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic diphosphoric anhydride (**26b**)*

Phosphonodiphosphate **26b** was prepared according to the procedure described for compound **23a**, starting from **5b** (45 mg; 0.12 mmol) in a yield of 14 mg (20%). HRMS $(M - H)^-$ for $C_{10}H_{14}O_{13}N_5FP_3$ calculated: 523.97905; measured: 523.97839; IR (KBr, cm^{-1}): 3455, 3303, 3126, 2963, 2876, 2760, 2361, 1696, 1654, 1606, 1534, 1378, 1252, 1215, 1129, 1094, 1077, 1003, 932, 799, 688, 637, 529, 479. For NMR data, see table IIa and IIb.

*4.30. ((((2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic diphosphoric anhydride (**26c**)*

Phosphonodiphosphate **26c** was prepared according to the procedure described for compound **26a,** starting from **1** (90 mg; 0.2 mmol) in a yield of 50 mg (45%).

Spectral data were in accordance with values from the literature [14].

*4.31. ((((2R,3S,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl)phosphonic diphosphoric anhydride (**26d**)*

Phosphonodiphosphate **26d** was prepared according to the procedure described for compound **26a,** starting from **6a** (180 mg; 0.39 mmol) in a yield of 150 mg (68%). HRMS $(M - H)^-$ for $C_{10}H_{15}O_{14}N_5P_3$ calculated: 521.98338; measured: 521.98242; IR (coating MeOH, cm^{-1}): 3432, 3313, 3098, 2346, 1695, 1650, 1533, 1449, 1232, 1128, 1073, 1032, 999, 895, 792, 688. For NMR data, see table IIa and IIb.

*4.32. ((((2R,3S,4R,5R)-5-(7-amino-3H-[1,2,3]triazolo[4,5-d] pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy)methyl) phosphonic diphosphoric anhydride (**26e**)*

Phosphonodiphosphate **26e** was prepared according to the procedure described for the compound **26a,** starting from **6b** (100 mg; 0.28 mmol) in a yield of 43 mg (28%). HRMS $(M - H)^-$ for $C_9H_{13}N_6Na_2O_{13}P_3$ calculated: 506.98372; measured: 506.98343; IR (KBr, cm-1): 3344, 3285, 3285, 3190, 1662, 1579, 1453, 1420, 1334, 1248, 1126, 1075, 1037, 1016, 904, 687, 648. For NMR data, see table IIa and IIb.

*4.33. ((((2R,3S,4R,5R)-5-(5-amino-7-hydroxy-3H-[1,2,3]triazolo [4,5-d]pyrimidin-3-yl)-3,4-dihydroxytetrahydrofuran-2-yl)oxy) methyl)phosphonic diphosphoric anhydride (**26f**)*

Phosphonodiphosphate **26f** was prepared according to the protocol developed for the compound **26a,** starting from **6c** (100 mg; 0.27 mmol) in a yield of 110 mg (80%). HRMS $(M - H)^-$ for $C_9H_{14}O_{14}N_6P_3$ calculated: 522.97863; measured: 522.97760; IR (KBr, cm^{-1}): 3402, 3387, 3163, 2493, 1709, 1644, 1533, 1456, 1227, 1109, 1070, 1036, 1001, 930, 788, 682; NMR: For NMR data, see table IIa and IIb.

*4.34. Butyl (((((2R,3R,4R,5R)-5-(6-amino-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)(phenoxy)phosphoryl)-L-phenylalaninate (**27a**)*

Triethylammonium salt of phosphonate **5a** (135 mg; 0.3 mmol) was converted to tetrabutylammonium salt (Dowex® 50WX 8 in tetrabutylammonium cycle) and dried by the co-evaporation with anhydrous pyridine. The solution of **5a**, L-phenylalanine butyl ester hydrochloride (137 mg; 0.53 mmol), phenol (125 mg; 1.3 mmol) and Et_3N (445 μL; 3.18 mmol) in dry pyridine (12 mL) was stirred for 15 min at 60 °C. Next, the solution of triphenylphosphine (412 mg; 1.57 mmol) and Aldrithiol™ (485 mg; 7.34 mmol) in dry pyridine (6 mL) was added to the mixture. The mixture was stirred for 16 h at 60 °C, and then concentrated. The solid residue was adsorbed on a silica gel in acetone, and phosphonoamidate **27a** was isolated by chromatography on a silica gel (0–8% EtOH in $CHCl_3$) in a yield of 85 mg (45%) as a mixture of epimers (estimated ratio by ^{31}P NMR 1:1). HRMS $(M + Na)^+$ for $C_{29}H_{34}FN_6O_7P$ calculated: 651.21028; measured: 651.20978; IR ($CHCl_3$, cm^{-1}): 3601, 3413, 3062, 2963, 2931, 2875, 2856, 1631, 1602, 1589, 1491, 1471, 1456, 1420, 1330, 1294, 1244, 1069, 1032, 901, 702, 690. For NMR data, see table IIa and IIb.

*4.35. Butyl (((((2R,3R,4R,5R)-5-(2-amino-6-hydroxy-9H-purin-9-yl)-4-fluoro-3-hydroxytetrahydrofuran-2-yl)oxy)methyl)(phenoxy) phosphoryl)-L-phenylalaninate (**27b**)*

Phosphonoamidate **27b** was prepared according to the procedure described for the compound **27a,** starting from **5b** (50 mg; 0.1 mmol) in a yield of 28 mg (43%) as a mixture of epimers. HRMS $(M + Na)^-$ for $C_{29}H_{34}O_8N_6FNaP$ calculated: 667.20520; measured: 667.20472; IR ($CHCl_3$, cm^{-1}): 3469, 3307, 3066, 2963, 2935, 2877, 1693, 1654, 1604, 1591, 1533, 1491, 1466, 1456, 1379, 1379, 1238, 1175, 1071, 1036, 701, 690, 642. For NMR data, see table IIa and IIb.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The work was supported by the European Regional Development Fund; OP RDE; Project: "Chemical biology for drugging undruggable targets (ChemBioDrug)" (No. CZ.02.1.01/0.0/0.0/16_019/0000729).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132159.

References

[1] E. De Clercq, A 40-year journey in search of selective antiviral chemotherapy, Annu. Rev. Pharmacol. Toxicol. 51 (2011) 1–24.

[2] I. Polakova, M. Budesinsky, Z. Tocik, I. Rosenberg, Tetrofuranose nucleoside phosphonic acids: synthesis and properties, Collect. Czech Chem. Commun. 76 (5) (2011) 503–536.

[3] Š. Králíková, M. Buděšínký, M. Masojídková, I. Rosenberg, Nucleoside 5′-C-phosphonates: reactivity of the α-hydroxyphosphonate moiety, Tetrahedron 62 (20) (2006) 4917–4932.

[4] O. Simak, P. Pachl, M. Fabry, M. Budesinsky, T. Jandusik, A. Hnizda, R. Sklenickova, M. Petrova, V. Veverka, P. Rezacova, J. Brynda, I. Rosenberg, Conformationally constrained nucleoside phosphonic acids - potent inhibitors of human mitochondrial and cytosolic 5[prime or minute](3[prime or minute])-nucleotidases, Org. Biomol. Chem. 12 (40) (2014) 7971–7982.

[5] C.U. Kim, B.Y. Luh, J.C. Martin, Regiospecific and highly stereoselective electrophilic addition to furanoid glycals: synthesis of phosphonate nucleotide analogs with potent activity against HIV, J. Org. Chem. 56 (8) (1991) 2642–2647.

[6] S. De, S. De Jonghe, P. Herdewijn, Synthesis of a 3'-Fluoro-3'-deoxytetrose adenine phosphonate, J. Org. Chem. 82 (18) (2017) 9464–9478 (Ahead of Print).

[7] Q. Li, E. Groaz, P. Herdewijn, Synthesis of tetradialdose phosphonate nucleosides as mimics of l-nucleotides, Tetrahedron 75 (37) (2019) 130497.

[8] C.G. Boojamra, R.L. Mackman, D.Y. Markevitch, V. Prasad, A.S. Ray, J. Douglas, D. Grant, C.U. Kim, T. Cihlar, Synthesis and anti-HIV activity of GS-9148 (2′-Fd4AP), a novel nucleoside phosphonate HIV reverse transcriptase inhibitor, Bioorg. Med. Chem. Lett 18 (3) (2008) 1120–1123.

[9] I. Gentile, F. Borgia, A.R. Buonomo, G. Castaldo, G. Borgia, A novel promising therapeutic option against hepatitis C virus: an oral nucleotide NS5B polymerase inhibitor sofosbuvir, Curr. Med. Chem. 20 (30) (2013) 3733–3742.

[10] H. Ren, H. An, P.J. Hatala, W.C. Stevens Jr., J. Tao, B. He, Versatile synthesis and biological evaluation of novel 3'-fluorinated purine nucleosides, Beilstein J. Org. Chem. 11 (2015) 2509–2520.

[11] G.G. Sivets, F. Amblard, R.F. Schinazi, Synthesis of 2-fluoro-substituted and 2,6-modified purine 2′,3′-dideoxy-2′,3′-difluoro-d-arabinofuranosyl nucleosides from d-xylose, Tetrahedron 75 (13) (2019) 2037–2046.

[12] R. Käppi, Z. Kazimierczuk, F. Seela, H. Lönnberg, Kinetics and mechanism for acid-catalyzed hydrolysis of regioisomeric 2′-deoxyribonucleosides of 8-azaadenine and substituted benzotriazoles, Nucleos Nucleot. 10 (1–3) (1991) 571–572.

[13] N.B. Dyatkina, F. Theil, M. von Janta-Lipinski, Stereocontrolled synthesis of the four stereoisomeric diphosphorylphosphonates of carbocyclic 2′,3′-dideoxy-2′,3′-didehydro-5′-noradenosine, Tetrahedron 51 (3) (1995) 761–772.

[14] Y.-h. Koh, J.H. Shim, J.Z. Wu, W. Zhong, Z. Hong, J.-L. Girardet, Design, synthesis, and antiviral activity of adenosine 5'-phosphonate analogues as chain terminators against hepatitis C virus, J. Med. Chem. 48 (8) (2005) 2867–2875.

[15] T. Klejch, D.T. Keough, M. Chavchich, J. Travis, J. Skácel, R. Pohl, Z. Janeba, M.D. Edstein, V.M. Avery, L.W. Guddat, D. Hocková, Sulfide, sulfoxide and sulfone bridged acyclic nucleoside phosphonates as inhibitors of the Plasmodium falciparum and human 6-oxopurine phosphoribosyltransferases: synthesis and evaluation, Eur. J. Med. Chem. 183 (2019) 111667.

[16] R.L. Mackman, A.S. Ray, H.C. Hui, L. Zhang, G. Birkus, C.G. Boojamra, M.C. Desai, J.L. Douglas, Y. Gao, D. Grant, G. Laflamme, K.-Y. Lin, D.Y. Markevitch, R. Mishra, M. McDermott, R. Pakdaman, O.V. Petrakovsky, J.E. Vela, T. Cihlar, Discovery of GS-9131: design, synthesis and optimization of amidate prodrugs of the novel nucleoside phosphonate HIV reverse transcriptase (RT) inhibitor GS-9148, Bioorg. Med. Chem. 18 (10) (2010) 3606–3617.

[17] G. Birkus, N. Kutty, C.R. Frey, R. Shribata, T. Chou, C. Wagner, M. McDermott, T. Cihlar, Role of cathepsin A and lysosomes in the intracellular activation of novel antipapillomavirus agent GS-9191, Antimicrob. Agents Chemother. 55 (5) (2011) 2166.

[18] K. Hercík, J. Kozak, M. Šála, M. Dejmek, H. Hřebabecký, E. Zborníková, M. Smola, D. Ruzek, R. Nencka, E. Boura, Adenosine triphosphate analogs can efficiently inhibit the Zika virus RNA-dependent RNA polymerase, Antivir. Res. 137 (2017) 131–133.

[19] A. Cho, L. Zhang, J. Xu, R. Lee, T. Butler, S. Metobo, V. Aktoudianakis, W. Lew, H. Ye, M. Clarke, E. Doerffler, D. Byun, T. Wang, D. Babusis, A.C. Carey, P. German, D. Sauer, W. Zhong, S. Rossi, M. Fenaux, J.G. McHutchison, J. Perry, J. Feng, A.S. Ray, C.U. Kim, Discovery of the first C-nucleoside HCV polymerase inhibitor (GS-6620) with demonstrated antiviral response in HCV infected patients, J. Med. Chem. 57 (5) (2014) 1812–1825.

[20] I. Mejdrová, D. Chalupská, M. Kögler, M. Šála, P. Plačková, A. Baumlová, H. Hřebabecký, E. Procházková, M. Dejmek, R. Guillon, D. Strunin, J. Weber, G. Lee, G. Birkus, H. Mertlíková-Kaiserová, E. Boura, R. Nencka, Highly selective phosphatidylinositol 4-kinase IIIβ inhibitors and structural insight into their mode of action, J. Med. Chem. 58 (9) (2015) 3767–3793.