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# Design, Synthesis, and Antiviral Activity of Novel Ribonucleosides of 1,2,3-Triazolylbenzyl-aminophosphonates

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A novel series of ribonucleosides of 1,2,3-triazolylbenzyl-aminophosphonates was synthesized through the Kabachnik–Fields reaction using $I_2$ as catalyst followed by copper-catalyzed cycloaddition of the azide–alkyne reaction (CuAAC). All structures of the newly prepared compounds were characterized by $^1$H NMR, $^{13}$C NMR, and HRMS spectra. The structures of **2e**, **2f**, **3d**, and **3g** were further confirmed by X-ray diffraction analysis. These compounds were tested against various strains of DNA and RNA viruses; compounds **4b** and **4c** showed a modest inhibitory activity against respiratory syncytial virus (RSV) and compound **4h** displayed modest inhibitory activity against Coxsackie virus B4.

**Keywords:** 1,2,3-Triazoles / α-Aminophosphonates / Antiviral activity / Kabachnik–Fields reaction / Ribonucleosides

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## Introduction

Currently, most of the human beings in the world suffer from different kinds of diseases caused by DNA and RNA viruses. These diseases are mostly diagnosed but difficult to cure. Vaccination is a reliable tool to fight viral diseases, but it is only available against few viruses. The difficulties associated with national or worldwide vaccination programs make antiviral chemotherapy an even more practical approach in the fight against epidemic viral infections. Nucleoside analogs are synthetic compounds that are structurally similar to natural nucleosides and can serve as building blocks of DNA and RNA. They can act as competitive inhibitors of viral and cellular DNA and RNA polymerases or alternatively can be incorporated into growing DNA and RNA strands causing chain termination [1].

α-Aminophosphonates are defined as structural analogs of natural amino acids. They are considered as an important class of compounds with diverse and interesting biological activities. Some of the aminophosphonates were described as anticancer agents [2], enzyme inhibitors [3], peptide mimetics [4], antibiotics and pharmacological agents [5]. They have also

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been reported to be interesting carriers for the transport of hydrophilic molecules across bilayer lipid membranes [6]. The α-aminophosphonate derivatives are often synthesized via the Kabachnik–Fields reaction by coupling of a carbonyl compound, an amine, and a hydroxyphosphoryl compound using various catalysts [7–9].

1,2,3-Triazoles were prepared by Huisgen in the 1960s [10] using the 1,3-dipolar cycloaddition reaction with acetylenes. After approximately four decades, this reaction has acquired considerable attention owing to the introduction of copper(I) as catalyst by Medal and then by Sharpless [11–13]. The copper-catalyzed cycloaddition of azides and alkynes (CuAAC) also known as "click chemistry" offers a simple access to the 1,4-isomer in very short reaction times.

Further, nucleosides containing 1,2,3-triazole ring have been of special interest in drug development research. Some synthetic triazoles have displayed interesting biological activities and several analogs have been tested against hepatitis C and HIV-1 viruses [14–18]. Moreover, nucleoside and acyclonucleoside analogs containing 1,2,3-triazole and phosphonate structures have been described as potent antiviral agents [19–21].

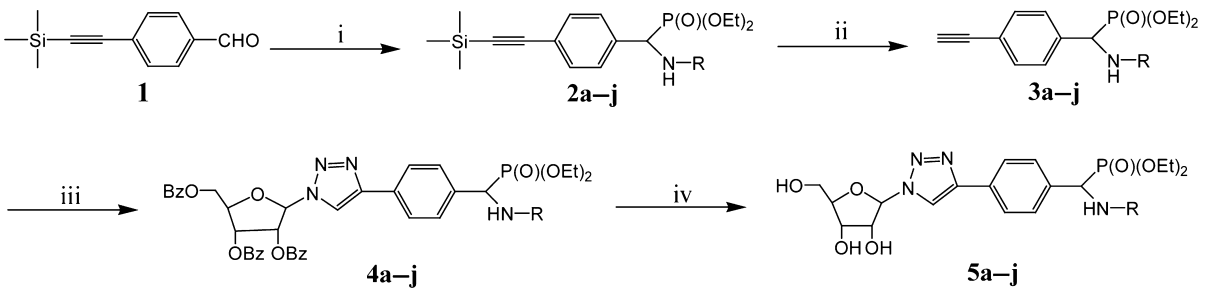
Herein, we describe the synthesis of novel hybrid molecules containing triazolyl-nucleoside linked to α-aminophosphonates by a phenyl ring. The choice of these structures is based on the combination of both pharmacophore parts, the phenyl-triazolyl-riboside and the α-aminophosphonates, which are known to have significant pharmacological properties. Our synthesis strategy is based on the use of two reactions: Kabachnick–Fields reaction and 1,3-dipolar cycloaddition. The compounds obtained were tested against selected DNA and RNA viruses.

## Results and discussion

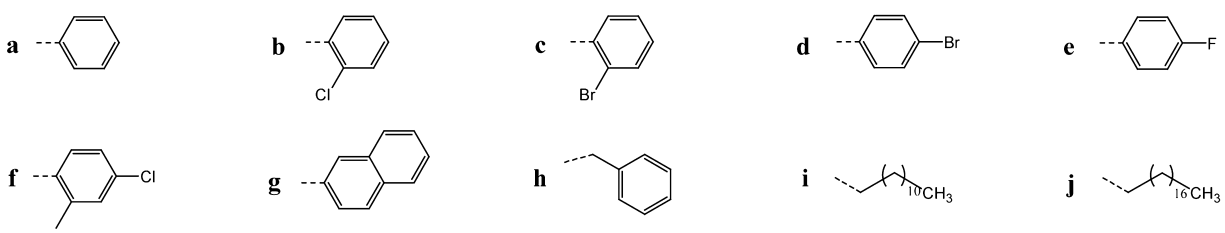
### Chemistry

The synthesis of the desired compounds (**4a–j** and **5a–j**) is depicted in Scheme 1. Initially, the α-aminophosphonate compounds were prepared in good yields via the Kabachnik–Fields reaction. The 4-[(trimethylsilyl)ethynyl]benzaldehyde **1** was reacted with diethylphosphite and corresponding amine in acetonitrile using molecular iodine as catalyst [22–24]. The latter is low-priced, readily available, non-metallic, and non-toxic. The mixture was stirred at room temperature for 1 h to get compounds **2a–j**. The next step is deprotection of the trimethylsilyl group. For this purpose, tetrabutylammonium fluoride (TBAF) in tetrahydrofurane (THF) was used to give the terminal alkyne [25]. The structures of **2e**, **2f**, **3d**, and **3g** were confirmed by X-ray diffraction (Fig. 1). According to the crystal data, the structures are similar for these compounds. The P–C bond has a staggered conformation, with the two six-membered groups with respect to the P=O double bond. The two benzene rings are almost perpendicular in all four compounds. In each crystal structure (**2e**, **3d**, and **3g)**, the molecules are arranged as centrosymmetric or pseudocentrosymmetric dimers related by two N–H···O=P hydrogen bonds. On the other hand, in the crystal structure of **2f**, the hydrogen bond N–H···O=P is not found, and the molecules are arranged as centrosymmetric dimers linked by $C_{methyl}$–H···O=P hydrogen bonds [26].

Next, the 1,2,3-triazolyl-nucleosides were prepared using the 1,3-dipolar cycloaddition reaction. For this, the terminal alkynes **3a–j** and β-azido-ribose [27] were coupled using the Cu alkyne-azide cycloaddition in basic medium (triethylamine) and the reaction was carried out under microwave




R for **2**, **3**, **4** and **5:**




**Scheme 1.** Reagents and conditions: (i) R-$NH_2$ (1.2 equiv.), H(O)P$(OEt)_2$ (1.2 equiv.), $I_2$ (0.2 equiv.), MeCN, r.t., 1 h; (ii) TBAF (1 equiv.), THF, r.t., 30 min; (iii) azido-ribose (2.5 equiv.), CuI (0.1 equiv.), $Et_3N$ (1.1 equiv.), MWI, 5 min; (iv) MeONa (1 equiv.), MeOH, r.t., 30 min.

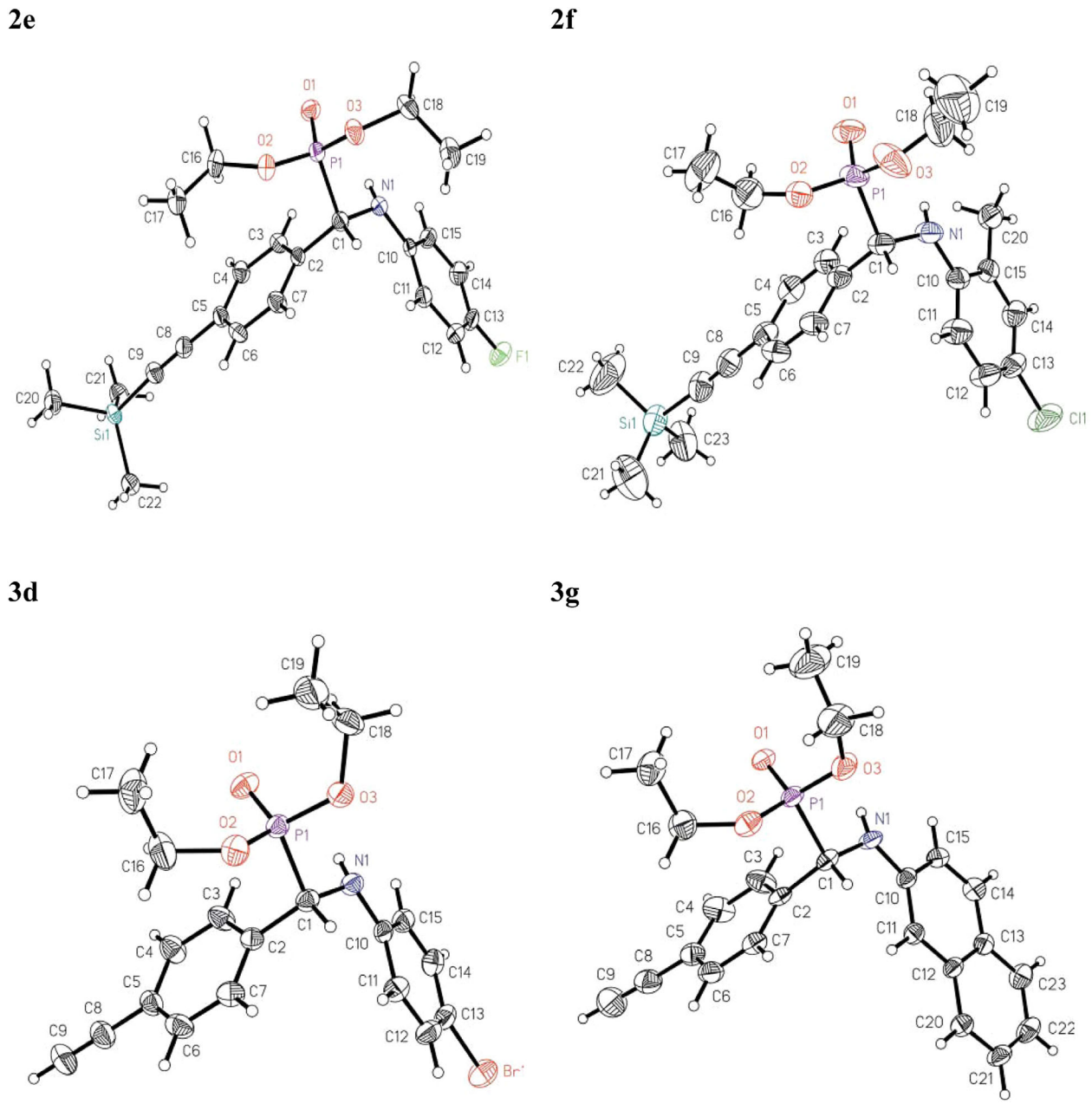
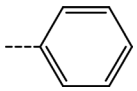
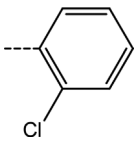
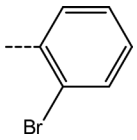
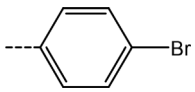
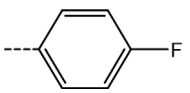
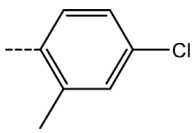
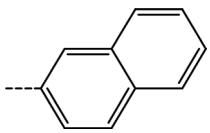
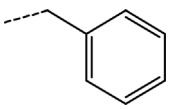
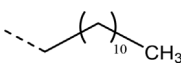
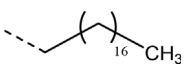



**Figure 1.** X-ray crystallographic structures of compounds **2e**, **2f**, **3d**, and **3g**. Displacement ellipsoids are drawn at the 50% probability level.

irradiation [28]. Microwave heating has been shown to increase reaction yields and to speed up reaction time [29], β-azido-ribose is slightly unstable under micro-wave conditions and was used in excess. The configuration at the anomeric carbon C1′ is retained as it is present in the β-azido-ribose. The hydroxyl functions were protected by benzoyl groups prior to the CuAAC reaction in order to increase the solubility of the compounds. The structures of all compounds were confirmed on the basis of $^{1}$H, $^{13}$C NMR spectra as well as by high-resolution mass spectrometry. In the $^{1}$H NMR spectra of the intermediates, the triazole proton appears as a singlet in the aromatic region while the anomeric proton appears as a multiplet around 6 ppm.

The last step involves the removal of the benzoyl protecting groups from O2′, O3′, and O5′ positions of D-ribose **4a–j** using sodium methoxide (NaOMe) in methanol [30] to afford the desired 1,2,3-triazole nucleosides **5a–j** (Table 1).

**Table 1.** Results of protected (4a–j) and deprotected (5a–j) triazolo nucleoside phosphonates.

| Entry | R | Compound[a)] | Yield[b)] (%) | Compound[a)] | Yield[c)] (%) |
|---|---|---|---|---|---|
| 1 |  | **4a** | 95 | **5a** | **98** |
| 2 |  | **4b** | 90 | **5b** | **99** |
| 3 |  | **4c** | 92 | **5c** | **98** |
| 4 |  | **4d** | 94 | **5d** | **99** |
| 5 |  | **4e** | 75 | **5e** | **95** |
| 6 |  | **4f** | 89 | **5f** | **98** |
| 7 |  | **4g** | 90 | **5g** | **98** |
| 8 |  | **4h** | 78 | **5h** | **95** |
| 9 |  | **4i** | 84 | **5i** | **96** |
| 10 |  | **4j** | 80 | **5j** | **97** |

[a)] All products were characterized by $^{1}H$ NMR, $^{13}C$ NMR, and mass spectrometry.
[b)] Yields of isolated products for the CuAAC reaction.
[c)] Yields of isolated products for the protection reaction.

## Biological testing

The antiviral activities of the synthesized compounds (**4a–j, 5a–j)** were tested against different viruses: HIV-1 and HIV-2 in MT4 cell cultures; herpes simplex virus-1 (HSV-1) (Kos strain), herpes simplex virus-2 (HSV-2) (G strain), HSV-1 thymidine kinase deficient, acyclovir-resistant ($TK^-$ Kos, $ACV^r$), vaccinia virus, vesicular stomatitis virus (VSV), adenovirus-2, varicella-zoster virus (VZV) (Oka strain and $TK^-$ 07/1 strain), human cytomegalovirus (HCMV) (AD-169 and Davis strain) in human embryonic lung (HEL) cells; VSV, Coxsackie virus B4, and respiratory syncytial virus (RSV) in HeLa cells; parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, and Punta Toro virus in Vero cells; feline corona virus (FIPV) and feline herpes virus in Crandell-Rees Feline Kidney (CRFK) cells,

influenza A H1N1 subtype, influenza A H3N2 subtype, and influenza B virus in MDCK (Madin–Darby canine kidney) cells. The following reference compounds were included: tenofovir (PMPA), AMD3100, ganciclovir, cidofovir, acyclovir, brivudin, the lectins *Hippeastrum* hybrid agglutinin (HHA) and *Urtica dioica* agglutinin (UDA), dextran sulfate (molecular weight 10000, DS-10000), ribavirin, oseltamivir carboxylate, amantadine and rimantadine, zalcitabine and alovudine. The antiviral activity was expressed as the $EC_{50}$: the compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%. The cytotoxicity of the tested compounds toward the uninfected host cells was defined as the minimum cytotoxic concentration (MCC) that causes a microscopically detectable alteration of normal cell morphology. The 50% cytotoxic concentration ($CC_{50}$), causing a 50% decrease in cell viability was determined using a colorimetric 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) assay system.

The tested compounds (**4a–j, 5a–j)** displayed no antiviral activity against the different viruses tested except for compounds **4b** and **4c** that showed a slight inhibition of respiratory syncytial virus replication (Table 2) and compounds **5c**, **5f**, and **5g** that displayed weak activity against both $TK^+$ and $TK^-$ VZV strains (see Supporting Information). Although compound **4h** had some activity against Coxsackie virus B4 in Vero cell cultures, no activity was seen in HeLa cells (Tables 2 and 3).

## Conclusion

A series of novel 1,2,3-triazolyl ribosides linked to α-aminophosphonates (**4a–j**, **5a–j**) were successfully prepared in high yield via the Kabachnik–Fields reaction and a Cu(I)-catalyzed alkyne-azide cycloaddition under microwave irradiation. The synthesized compounds were evaluated against a broad range of DNA and RNA viruses, some of them showing modest activity against respiratory syncytial virus (compounds **4b** and **4c**) and varicella-zoster virus (compounds **5c**, **5f**, and **5g)**.

## Experimental

### Chemistry

*General*

Reactions were carried out in a microwave oven model AVM510/WP/WH. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck, Darmstadt, Germany); UV light was used for visualization of the spots. All products were purified by column chromatography on silica gel (100–200 mesh; Merck). $^1$H NMR and

**Table 2.** **Cytotoxicity and antiviral activity of some compounds in HeLa cell cultures.**

| Compound | Minimum cytotoxic concentration[a] (μM) | $EC_{50}$[b] (μM) | | |
|---|---|---|---|---|
| | | Vesicular stomatitis virus | Coxsackie virus B4 | Respiratory syncytial virus |
| **4a** | >50 | >50 | >50 | >50 |
| **4b** | >100 | >100 | >100 | 47.5 ± 3.5 |
| **4c** | >100 | >100 | >100 | 51.5 ± 9.2 |
| **4d** | >100 | >100 | >100 | ≥72.5 ± 38.9 |
| **5i** | 20 | >4 | >4 | >4 |
| **5j** | ≥20 | >20 | >20 | >20 |
| DS-10.000 (μg/mL) | >100 | 12 | >100 | 1.3 ± 0.7 |
| Ribavirin | >250 | 22 | 146 | 2.9 ± 1.3 |

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

**Table 3.** **Cytotoxicity and antiviral activity of 4h in Vero cell cultures.**

| Compound | Minimum cytotoxic concentration[a] (μM) | $EC_{50}$[b] (μM) | | | | |
|---|---|---|---|---|---|---|
| | | Parainfluenza-3 virus | Reovirus-1 | Sindbis virus | Coxsackie virus B4 | Punta Toro virus |
| **4h** | >100 | >100 | >100 | >100 | 20 | >100 |
| DS-10.000 (μg/mL) | >100 | >100 | >100 | 8.9 | >100 | 8.9 |
| Ribavirin | >250 | 85 | >250 | >250 | >250 | 112 |

[a] Required to cause a microscopically detectable alteration of normal cell morphology.
[b] Required to reduce virus-induced cytopathogenicity by 50%.

$^{13}$C NMR spectra were recorded on a Bruker 300 and 75 MHz spectrometer, respectively, $SiMe_4$ was used as internal standard. Chemical shifts are given in ppm and coupling constants (*J*) in MHz and multiplicity is reported as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were produced by ESI/MS and MALDI-TOF-MS.

*General procedure for the synthesis of diethyl [(4-(2-(trimethylsilyl)ethynyl)phenyl)(aryl or alkylamino)methyl]-phosphonates **2a–j***

The compounds **2a–j** were synthesized by reaction of commercial (Sigma–Aldrich) 4-[(trimethylsilyl)ethynyl]benzaldehyde **1** (1 mmol), diethylphosphite (1.2 equiv.), and corresponding amine (1.2 equiv.) in acetonitrile (3 mL) using molecular iodine (0.2 equiv.) as catalyst at room temperature, the reaction mixture was stirred at room temperature for 1 h. Then, the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography using ethyl acetate/hexane as eluent.

*Diethyl [(4-(2-(trimethylsilyl)ethynyl)phenyl)-(phenylamino)methyl]phosphonate **2a***

Yield: 95%; Rf: 0.40; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.22 (s, 9H, –$CH_3$), 1.06 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.20 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 3.60–3.68 (m, 1H, –$OCH_2$–), 3.83–3.92 (m, 1H, –$OCH_2$–), 3.97–4.08 (m, 2H, –$OCH_2$–), 4.62 (d, 1H, CHP, $J = 23.7$ Hz), 5.17 (s, 1H, NH), 6.47 (d, 2H, Ar–H, $J = 8.1$ Hz), 6.61 (t, 1H, Ar–H, $J = 7.2$ Hz), 7.01 (t, 2H, Ar–H, $J = 7.8$ Hz), 7.33–738 (m, 4H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.06 (Si–$CH_3$), 16.32–16.58 ($CH_3$), 55.20 (CHP), 63.43–63.52 ($CH_2$), 94.74, 104.86 (≡C–), 114.01, 118.69, 127.84, 129.28, 132.26 (phenyl–CH), 122.81, 136.76, 146.35 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{22}H_{30}NO_3PSi$: 415.54, found: 417.00; HRMS (M+K): calcd. for $C_{22}H_{30}NO_3PSiK$: 454.13642, found: 454.13539.

*Diethyl [2-chlorophenylamino][(4-(2-(trimethylsilyl)-ethynyl)phenyl]methylphosphonate **2b***

Yield: 90%; Rf: 0.45; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.10 (s, 9H, –$CH_3$), 1.02 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.10 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 3.56 (m, 1H, –$OCH_2$–), 3.81 (m, 1H, –$OCH_2$–), 3.95 (m, 2H, –$OCH_2$–), 4.54 (d, 1H, CHP, $J = 24.3$ Hz), 5.14 (br s, 1H, NH), 6.15 (d, 1H, Ar–H, $J = 7.8$ Hz), 6.63 (t, 1H, Ar–H, $J = 7.2$ Hz), 6.71 (t, 2H, Ar–H, $J = 7.5$ Hz), 6.93–7.19 (m, 4H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.07–16.50 ($CH_3$), 54.99 (CHP), 63.15–63.68 ($CH_2$), 94.83, 104.76 (≡C–), 112.73, 117.82, 118.78, 122.42, 127.06, 127.70, 129.39, 132.46 (phenyl–CH), 122.96 (C–Cl), 120.08, 136.06, 142.29 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{22}H_{29}ClNO_3PSi$: 449.98, found: 451.00; HRMS (M+K): calcd. for $C_{22}H_{29}ClNO_3PSiK$: 488.09744, found: 488.09631.

*Diethyl [2-bromophenylamino][(4-(2-(trimethylsilyl)-ethynyl)phenyl]methylphosphonate **2c***

Yield: 89%; Rf: 0.45; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.10 (s, 9H, –$CH_3$), 0.99 (t, 3H, –$CH_3$, $J = 7.2$ Hz), 1.07 (t, 3H, –$CH_3$, $J = 7.2$ Hz), 3.57 (m, 1H, –$OCH_2$–), 3.76 (m, 1H, –$OCH_2$–), 3.91 (m, 2H, –$OCH_2$–), 4.54 (d, 1H, CHP, $J = 24.6$ Hz), 5.21 (br s, 1H, NH), 6.12 (d, 1H, Ar–H, $J = 8.1$ Hz), 6.63 (t, 1H, Ar–H, $J = 7.5$ Hz), 6.71 (t, 2H, Ar–H, $J = 7.5$ Hz), 7.15–7.29 (m, 4H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.30–16.52 ($CH_3$), 55.20 (CHP), 63.43–63.72 ($CH_2$), 94.83, 104.76 (≡C–), 110.57 (C–Br), 112.77, 119.27, 127.60, 128.36, 132.46–132.52 (phenyl–CH), 122.87, 135.91, 143.07 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{22}H_{29}BrNO_3PSi$: 494.43, found: 496.00; HRMS (M+Na): calcd. for $C_{22}H_{29}BrNO_3PSiNa$: 516.07299, found: 516.07122.

*Diethyl [4-bromophenylamino][(4-(2-(trimethylsilyl)-ethynyl)phenyl]methylphosphonate **2d***

Yield: 92%; Rf: 0.40; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.02 (s, 9H, –$CH_3$), 0.92 (t, 3H, –$CH_3$, $J = 6.3$ Hz), 1.02 (t, 3H, –$CH_3$, $J = 6.3$ Hz), 3.49 (m, 1H, –$OCH_2$–), 3.71 (m, 1H, –$OCH_2$–), 3.88 (m, 2H, –$OCH_2$–), 4.42 (d, 1H, CHP, $J = 24.3$ Hz), 4.65 (br s, 1H, NH), 6.17 (d, 2H, Ar–H, $J = 9.0$ Hz), 6.93 (d, 2H, Ar–H, $J = 8.7$ Hz), 7.12 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.19 (d, 2H, Ar–H, $J = 8.1$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.28–16.53 ($CH_3$), 55.15 (CHP), 63.44–63.67 ($CH_2$), 94.98, 104.62 (≡C–), 110.49 (C–Br), 115.58, 127.70, 131.98–132.36 (phenyl–CH), 122.95, 136.02, 145.11 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{22}H_{29}BrNO_3PSi$: 494.43, found: 494.90; HRMS (M+Na): calcd. for $C_{22}H_{29}BrNO_3PSiNa$: 516.07299, found: 516.07251.

*Diethyl [4-fluorophenylamino][(4-(2-(trimethylsilyl)-ethynyl)phenyl]methylphosphonate **2e***

Yield: 77%; Rf: 0.36; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.01 (s, 9H, –$CH_3$), 0.91 (t, 3H, –$CH_3$, $J = 6.7$ Hz), 1.07 (t, 3H, –$CH_3$, $J = 6.7$ Hz), 3.44 (m, 1H, –$OCH_2$–), 3.74 (m, 1H, –$OCH_2$–), 3.87 (m, 2H, –$OCH_2$–), 4.44 (d, 1H, CHP, $J = 24.3$ Hz), 5.20 (br s, 1H, NH), 6.25 (d, 2H, Ar–H, $J = 6.6$ Hz), 6.55 (d, 2H, Ar–H, $J = 6.6$ Hz), 7.15–7.22 (m, 4H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.25–16.51 ($CH_3$), 55.73 (CHP), 63.55–63.64 ($CH_2$), 94.87, 104.70 (≡C–), 114.95–115.84, 127.82, 132.31 (phenyl–CH), 122.87, 136.32, 142.58 (phenyl–C), 154.84 (C–F). ESI-MS (M+H), *m/z* calcd. for $C_{22}H_{29}FNO_3PSi$: 433.53, found: 434.80; HRMS (M+K): calcd. for $C_{22}H_{29}FNO_3PSiK$: 472.12699, found: 472.12658.

*Diethyl [4-chloro-2-methylphenylamino][(4-(2-(trimethylsilyl)ethynyl)phenyl]methylphosphonate **2f***

Yield: 87%; Rf: 0.43; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.01 (s, 9H, –$CH_3$), 0.89 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.02 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.99 (s, 3H, Ar–$CH_3$), 3.48 (m, 1H, –$OCH_2$–), 3.72 (m, 1H, –$OCH_2$–), 3.86 (m, 2H, –$OCH_2$–), 4.43 (d, 1H, CHP, $J = 24.6$ Hz), 4.54 (s, 1H, NH), 6.00 (d, 1H, Ar–H, $J = 8.4$ Hz), 6.93 (d, 1H, Ar–H, $J = 8.4$ Hz), 6.76 (s, 1H, Ar–H), 7.14–7.22 (m, 4H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.26–16.51, 17.38 ($CH_3$), 55.26 (CHP), 63.40–63.53 ($CH_2$), 94.81, 104.74 (≡C–), 124.81 (C–Cl), 112.56, 126.58, 127.59, 129.96–132.28 (phenyl–CH), 122.90, 136.27, 142.92 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for

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$C_{23}H_{31}ClNO_3PSi$: 464.01, found: 465.10; HRMS (M+K): calcd. for $C_{23}H_{31}ClNO_3PSiK$: 502,11309, found: 502.11199.

*Diethyl (4-(2-(trimethylsilyl)ethynyl)phenyl)(2-naphthalenylamino)methylphosphonate* ***2g***
Yield: 88%; Rf: 0.50; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.26 (s, 9H, –$CH_3$), 1.18 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.31 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 3.78 (m, 1H, –$OCH_2$–), 4.01 (m, 1H, –$OCH_2$–), 4.15 (m, 2H, –$OCH_2$–), 4.94 (d, 1H, CHP, $J = 24.3$ Hz), 6.10 (br s, 1H, NH), 6.69 (s, 1H, Ar–H), 6.61 (d, 1H, Ar–H, $J = 7.2$ Hz), 7.20–7.74 (m, 9H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 16.13–16.52 ($CH_3$), 55.09 (CHP), 63.00–63.64 ($CH_2$), 94.77, 104.80 (≡C–), 106.48, 118.16, 122.80, 126.12, 127.69–132.30 (phenyl–CH), 123.97, 126.85, 134.74, 136.43, 143.99 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{26}H_{32}NO_3PSi$: 465.60, found: 467.20; HRMS (M+Na): calcd. for $C_{26}H_{32}NO_3PSiNa$: 488.17813, found: 488.17658.

*Diethyl (benzylamino)(4-(2-(trimethylsilyl)ethynyl)phenyl)-methylphosphonate* ***2h***
Yield: 78%; Rf: 0.50; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.70 (s, 9H, –$CH_3$), 0.97 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.10 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 2.27 (br s, 1H, NH), 3.31 (d, 1H, CHP, $J = 24.5$ Hz), 3.64 (m, 2H, –$CH_2$–NH–), 3.78–3.98 (m, 4H, –$OCH_2$–), 7.04–7.13 (m, 5H, Ar–H), 7.20 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.33 (d, 2H, Ar–H, $J = 8.1$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.06 (Si–$CH_3$), 16.25–16.48 ($CH_3$), 51.08 ($CH_2$–N), 58.40 (CHP), 61.75–63.10 ($CH_2$), 94.54, 104.87 (≡C–), 127.22, 128.33–132.08 (phenyl–CH), 122.65, 136.42–139.10 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{23}H_{32}NO_3PSi$: 429.56, found: 431.00; HRMS (M+H): calcd. for $C_{23}H_{32}NO_3PSi$: 430.19618, found: 430.19647.

*Diethyl (dodecylamino)(4-(2-(trimethylsilyl)ethynyl)-phenyl)methylphosphonate* ***2i***
Yield: 88%; Rf: 0.40; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.07 (s, 9H, –$CH_3$), 0.63 (m, 6H, –$OCH_2CH_3$, –$CH_3$), 0.87–1.24 (m, 23H, –$CH_2$–, –$OCH_2CH_3$), 2.25 (m, 2H, –$CH_2$–NH–), 3.18 (br s, 1H, NH), 3.68–3.93 (m, 4H, –$OCH_2$–), 5.26 (d, 1H, CHP, $J = 23.4$ Hz), 7.17 (d, 2H, Ar–H, $J = 8.2$ Hz), 7.59 (d, 2H, Ar–H, $J = 8.2$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 14.00, 16.25–16.48 ($CH_3$), 22.50, 27.00, 29.11–37.56 ($CH_2$), 59.56 (CHP), 63.09–63.25 ($CH_2$), 94.54, 104.87 (≡C–), 128.64, 132.05 (phenyl–CH), 123.06, 135.00 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{28}H_{50}NO_3PSi$: 507.76, found: 509.40; HRMS (M+H): calcd. for $C_{28}H_{50}NO_3PSi$: 508.33703, found: 508.33659.

*Diethyl (octadecylamino)(4-(2-(trimethylsilyl)ethynyl)-phenyl)methylphosphonate* ***2j***
Yield: 86%; Rf: 0.40; Eluent: ethyl acetate/hexane, 7:3 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.25 (t, 9H, –$CH_3$), 0.86 (m, 6H, –$OCH_2CH_3$, –$CH_3$), 1.05–1.70 (m, 35H, –$CH_2$–, –$OCH_2CH_3$), 2.53 (m, 2H, –$CH_2$–NH–), 3.43 (br s, 1H, NH), 3.78–4.16 (m, 4H, –$OCH_2$–, CHP), 7.36 (d, 2H, Ar–H, $J = 8.2$ Hz), 7.62 (d, 2H, Ar–H, $J = 8.2$ Hz). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 0.00 (Si–$CH_3$), 14.19, 16.00–16.50 ($CH_3$), 22.74, 26.88–27.23, 29.51–30.30, 32.06, 29.11–37.56 ($CH_2$), 59.50 (CHP), 63.00–63.50 ($CH_2$), 94.50, 104.00 (≡C–), 128.50, 132.00 (phenyl–CH), 123.00, 135.00 (phenyl–C). ESI-MS (M+H), *m/z* calcd. for $C_{34}H_{62}NO_3PSi$: 591.92, found: 593.50; HRMS (M+H): calcd. for $C_{34}H_{62}NO_3PSi$: 592.43093, found: 592.42999.

*General procedure for the synthesis of diethyl [(4-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)(aryl or alkylamino)(phenyl)methyl]phosphonates* ***4a–j***
The trimethylsilyl ethynyl phenyl α-aminophosphonates **2** (0.7 mmol) were reacted with tetrabutylammonium fluoride (1 equiv.) in tetrahydrofurane (2.5 mL). After 30 min of stirring at room temperature, the reaction mixture was purified by silica gel column chromatography to get ethynyl phenyl α-aminophosphonates (**3a–j**).

The terminal alkyne **3** (0.5 mmol) and β-azido-ribose (2.5 equiv.) and triethyl amine (1.1 equiv.) were mixed with CuI (0.1 equiv.). The reaction mixture was homogenized in dry acetonitrile (1 mL) and stirred for 5 min. The solvent was evaporated under vacuum. The reaction mixture was then irradiated at the power level 400 W for 2–5 min. The residue was purified on silica gel using ethyl acetate/hexane as eluent.

*Diethyl [(4-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(phenylamino)methyl]-phosphonate* ***4a***
Yield: 95%; Rf: 0.45; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.11 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.26 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 3.72 (m, 1H, –$OCH_2$–), 3.95 (m, 1H, –$OCH_2$–), 4.11 (m, 2H, –$OCH_2$–), 4.60 (m, 1H, $H_{5'}$), 4.77 (d, 1H, CHP, $J = 25.2$ Hz), 4.85–4.91 (m, 1H, $H_{5'}$,$H_{4'}$, $H_{3'}$, NH), 6.16 (m, 1H, $H_{2'}$), 6.30 (m, 1H, $H_{1'}$), 6.53–6.74 (m, 4H, Ar–H), 7.13 (m, 2H, Ar–H), 7.31–7.68 (m, 12H, Ar–H, CH–triazole), 7.89–8.08 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 15.54, 15.80 ($CH_3$), 54.30 (CHP), 62.64–62.76 (C5′, $CH_2$), 70.87 (C2′), 74.61 (C3′), 80.58 (C4′), 89.73 (C1′), 113.26, 117.87, 125.30, 127.86, 128.52, 129.13, 133.05 (phenyl–CH, triazole–CH), 135.51, 145.66, 147.22 (phenyl–C, triazole–C), 164.37, 164.48, 165.40 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{45}H_{43}N_4O_{10}P$: 830.82, found: 831.40; HRMS (M+K): calcd. for $C_{45}H_{43}N_4O_{10}PK$: 869.23484, found: 869.23435.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(2-chlorophenylamino)methyl]-phosphonate* ***4b***
Yield: 90%; Rf: 0.45; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.12 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 1.29 (t, 3H, –$CH_3$, $J = 6.9$ Hz), 3.70 (m, 1H, –$OCH_2$–), 3.81 (m, 1H, –$OCH_2$–), 3.95–4.23 (m, 2H, –$OCH_2$–), 4.61 (m, 1H, $H_{5'}$), 4.77–4.90 (m, 3H, CHP, $H_{5'}$,$H_{4'}$), 5.45 (m, 1H, $H_{3'}$), 5.70 (br s, 1H, NH), 6.17 (m, 1H, $H_{2'}$), 6.30 (m, 1H, $H_{1'}$), 6.46–6.66 (m, 3H, Ar–H), 6.86–6.98 (m, 2H, Ar–H), 7.15–7.67 (m, 12H, Ar–H, CH–triazole), 7.88–8.05 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.25, 16.48 ($CH_3$), 54.85 (CHP), 63.15–63.64 (C5′, $CH_2$), 71.56 (C2′), 75.29 (C3′), 81.21 (C4′), 90.41 (C1′),

112.76, 117.66, 118.67, 122.33, 126.03, 128.18, 128.64, 129.35, 133.73 (phenyl–CH, triazole–CH), 120.09 (C–Cl), 135.56, 142.19, 147.78 (phenyl–C, triazole–C), 165.36, 165.40, 166.47 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{45}H_{42}ClN_4O_{10}P$: 865.26, found: 865.50; HRMS (M+K): calcd. for $C_{45}H_{42}ClN_4O_{10}PK$: 903.19587, found: 903.19617.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(2-bromophenylamino)methyl]-phosphonate* ***4c***

Yield: 92%; Rf: 0.45; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.09–1.25 (t, 6H, $-CH_3$), 3.79 (m, 1H, $-OCH_2-$), 3.92 (m, 1H, $-OCH_2-$), 3.94–3.99 (m, 2H, $-OCH_2-$), 4.52 (m, 1H, $H_{5'}$), 4.67–4.82 (m, 4H, CHP, NH, $H_{5'}$,$H_{4'}$), 5.45 (m, 1H, $H_{3'}$), 6.04 (m, 1H, $H_{2'}$), 6.19 (m, 1H, $H_{1'}$), 6.33–6.66 (m, 3H, Ar–H), 6.94 (m, 2H, Ar–H), 7.19–7.46 (m, 12H, Ar–H, CH–triazole), 7.79–8.03 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.27, 16.50 ($CH_3$), 55.08 (CHP), 63.43–63.69 (C5′, $CH_2$), 71.55 (C2′), 75.24 (C3′), 81.27 (C4′), 90.41 (C1′), 110.59 (C–Br), 112.81, 118.53, 119.16, 126.05, 128.12–129.89, 132.51, 133.50 (phenyl–CH, triazole–CH), 135.52, 143.19–147.83 (phenyl–C, triazole–C), 165.04–166.08 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{45}H_{42}BrN_4O_{10}P$: 909.71, found: 910.70; HRMS (M+K): calcd. for $C_{45}H_{42}BrN_4O_{10}PK$: 947.14535, found: 947.14589.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(4-bromophenylamino)methyl]-phosphonate* ***4d***

Yield: 94%; Rf: 0.45; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.11 (t, 3H, $-CH_3$, $J = 6.3$ Hz), 1.29 (t, 3H, $-CH_3$, $J = 6.3$ Hz), 3.69 (m, 1H, $-OCH_2-$), 3.93 (m, 1H, $-OCH_2-$), 4.12 (m, 2H, $-OCH_2-$), 4.59 (m, 1H, $H_{5'}$), 4.70 (d, 1H, CHP, $J = 24.3$ Hz), 4.78–4.89 (m, 3H, $H_{5'}$, $H_{4'}$, $H_{3'}$), 5.20 (br s, 1H, NH), 6.17 (m, 1H, $H_{2'}$), 6.31 (m, 1H, $H_{1'}$), 6.54 (m, 3H, Ar–H), 7.15 (m, 2H, Ar–H), 7.31–7.63 (m, 12H, Ar–H, CH–triazole), 7.85–8.07 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.21, 16.48 ($CH_3$), 54.85 (CHP), 63.38–63.60 (C5′, $CH_2$), 71.59 (C2′), 75.25 (C3′), 81.20 (C4′), 90.41 (C1′), 110.16 (C–Br), 115.56, 118.82, 126.03, 128.27–129.86, 131.87, 133.71 (phenyl–CH, triazole–CH), 135.67, 145.32–147.74 (phenyl–C, triazole–C), 165.04–166.06 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{45}H_{42}BrN_4O_{10}P$: 909.71, found: 911.30; HRMS (M+Na): calcd. for $C_{45}H_{42}BrN_4O_{10}PNa$: 931.17141, found: 931.17355.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(4-fluorophenylamino)methyl]-phosphonate* ***4e***

Yield: 75%; Rf: 0.40; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.12 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 1.30 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 3.72 (m, 1H, $-OCH_2-$), 3.97 (m, 1H, $-OCH_2-$), 4.13 (m, 2H, $-OCH_2-$), 4.60 (m, 1H, $H_{5'}$), 4.78–4.89 (m, 4H, CHP, $H_{5'}$, $H_{4'}$, $H_{3'}$), 5.15 (br s, 1H, NH), 6.16 (m, 1H, $H_{2'}$), 6.30 (m, 1H, $H_{1'}$), 6.54 (m, 3H, Ar–H), 6.82 (m, 2H, Ar–H), 7.32–7.67 (m, 12H, Ar–H, CH–triazole), 7.91–8.10 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.22–16.48 ($CH_3$), 55.60 (CHP), 63.33–63.51 (C5′, $CH_2$), 71.59 (C2′), 75.28 (C3′), 81.25 (C4′), 90.42 (C1′), 114.88–115.81, 118.63, 126.03, 128.28–129.88, 133.45, 133.88 (phenyl–CH, triazole–CH), 135.96, 142.46–147.83 (phenyl–C), 154.76 (triazole–C), 157.89 (C–F), 165.06–166.08 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{45}H_{42}FN_4O_{10}P$: 848.81, found: 849.10; HRMS (M+K): calcd. for $C_{45}H_{42}FN_4O_{10}PK$: 887.22542, found: 887.22670.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(4-chloro-2-methylphenylamino)-methyl]phosphonate* ***4f***

Yield: 89%; Rf: 0.40; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.13 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 1.29 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 2.28 (s, 3H, Ar–$CH_3$), 3.75 (m, 1H, $-OCH_2-$), 3.98 (m, 1H, $-OCH_2-$), 4.15 (m, 2H, $-OCH_2-$), 4.59 (m, 1H, $H_{5'}$), 4.63–4.90 (m, 4H, CHP, $H_{5'}$, $H_{4'}$, $H_{3'}$), 5.10 (br s, 1H, NH), 6.17 (m, 1H, $H_{2'}$), 6.30 (m, 2H, Ar–H), 6.54 (m, 1H, $H_{1'}$), 6.91 (d, 1H, Ar–H, $J = 8.4$ Hz), 7.03 (s, 1H, Ar–H), 7.33–7.65 (m, 12H, Ar–H, CH–triazole), 7.90–8.05 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.23–16.49, 17.40 ($CH_3$), 55.13 (CHP), 60.35, 63.36–63.46 (C5′, $CH_2$), 71.59 (C2′), 75.25 (C3′), 81.22 (C4′), 90.41 (C1′), 112.52, 118.72, 126.05, 128.07–129.94, 133.43–133.87 (phenyl–CH, triazole–CH), 122.80 (C–Cl), 135.79–142.99 (phenyl–C), 147.76 (triazole–C), 165.04–166.06 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{46}H_{44}ClN_4O_{10}P$: 879.29, found: 880.00; HRMS (M+K): calcd. for $C_{46}H_{44}ClN_4O_{10}PK$: 917.21206, found: 917.21196.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(2-naphthalenylamino)methyl]-phosphonate* ***4g***

Yield: 90%; Rf: 0.45; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.98 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 1.19 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 3.61 (m, 1H, $-OCH_2-$), 3.84 (m, 1H, $-OCH_2-$), 4.03 (m, 2H, $-OCH_2-$), 4.45 (m, 1H, $H_{5'}$), 4.65–4.88 (m, 3H, CHP, $H_{5'}$, $H_{4'}$), 5.19 (br s, 1H, NH), 6.03 (m, 1H, $H_{3'}$), 6.19 (m, 1H, $H_{2'}$), 6.38 (d, 1H, $H_{1'}$, $J = 3.3$ Hz), 6.61 (s, 1H, Ar–H), 6.90–7.53 (m, 19H, Ar–H, CH–triazole), 7.76–7.89 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.33–16.51 ($CH_3$), 54.91 (CHP), 56.91, 63.45–63.59 (C5′, $CH_2$), 71.59 (C2′), 75.26 (C3′), 81.21 (C4′), 90.41 (C1′), 106.50, 118.20, 118.78, 122.51, 126.34, 127.58–129.88, 133.43–133.86 (phenyl–CH, triazole–CH), 134.78, 136.00, 143.92–144.12 (phenyl–C), 147.84 (triazole–C), 165.03–166.06 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{49}H_{45}N_4O_{10}P$: 880.88, found: 882.00; HRMS (M+H): calcd. for $C_{49}H_{45}N_4O_{10}P$: 919.25049, found: 919.24998.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(benzylamino)methyl]-phosphonate* ***4h***

Yield: 78%; Rf: 0.40; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.08 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 1.21 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 3.06 (br s, 1H, NH), 3.48 (d, 1H, CHP, $J = 23.4$ Hz), 3.72 (m, 2H, $-CH_2-NH-$), 3.76–4.02 (m, 4H, $-OCH_2-$), 4.55 (m, 1H, $H_{5'}$), 4.77–4.82 (m, 2H, $H_{4'}$, $H_{5'}$), 6.06 (m, 1H, $H_{3'}$), 6.21 (m, 1H, $H_{2'}$), 6.46 (m, 1H, $H_{1'}$, $J = 3.6$ Hz), 7.17–

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7.47 (m, 16H, Ar–H, CH–triazole), 7.60 (d, 2H, Ar–H, $J = 7.8$ Hz), 7.76–7.89 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.32–16.48 ($CH_3$), 51.28 (CHP), 62.92–63.57 (C5′, $CH_2$), 71.64 (C2′), 75.28 (C3′), 81.26 (C4′), 90.42 (C1′), 118.56, 125.89, 127.18, 128.36–129.89, 133.47–133.88 (phenyl–CH, triazole–CH), 135.50, 139.19 (phenyl–C), 148.01 (triazole–C), 165.07–166.09 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{46}H_{45}N_4O_{10}P$: 844.84, found: 845.40; HRMS (M+K): calcd. for $C_{46}H_{45}N_4O_{10}PK$: 883.25049, found: 883.24988.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(dodecylamino)methyl]-phosphonate* ***4i***

Yield: 84%; Rf: 0.50; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.68 (t, 3H, $-CH_3$, $J = 6.6$ Hz), 0.97 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 0.99–1.32 (m, 23H, $-CH_3$, $-CH_2-$), 2.31 (m, 2H, $-CH_2-$NH–), 3.01 (br s, 1H, NH), 3.67 (m, 1H, $-OCH_2-$), 3.73–3.99 (m, 4H, $-OCH_2-$, CHP), 4.42 (m, 1H, $H_{5'}$), 4.77–4.82 (m, 2H, $H_{4'}$, $H_{5'}$), 5.97 (m, 1H, $H_{3'}$), 6.11 (m, 1H, $H_{2'}$), 6.45 (d, 1H, $H_{1'}$, $J = 4.0$ Hz), 7.19–7.44 (m, 13H, Ar–H, CH–triazole), 7.77–7.89 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 14.50, 16.32–16.47 ($CH_3$), 22.50, 27.00, 28.72–33.87, 40.21 ($CH_2$), 55.00 (CHP), 63.00–63.49 (C5′, $CH_2$), 71.59 (C2′), 75.28 (C3′), 81.31 (C4′), 90.48 (C1′), 119.16, 124.79, 125.71, 126.50, 127.42–133.88 (phenyl–CH, triazole–CH), 135.88–136.76 (phenyl–C), 147.50 (triazole–C), 165.00–166.00 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{51}H_{63}N_4O_{10}P$: 923.04, found: 924.00.

*Diethyl [(4-(1-(2,3,5-tri-O-benzoyl-β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)phenyl)(octadecylamino)methyl]-phosphonate* ***4j***

Yield: 80%; Rf: 0.50; Eluent: ethyl acetate/hexane, 8:2 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.77 (t, 3H, $-CH_3$, $J = 6.6$ Hz), 1.06–1.41 (m, 38H, $-CH_3$, $-CH_2-$), 2.39 (m, 2H, $-CH_2-$NH–), 3.05 (br s, 1H, NH), 3.73 (m, 1H, $-OCH_2-$), 3.84–4.01 (m, 4H, $-OCH_2-$, CHP), 4.53 (m, 1H, $H_{5'}$), 4.80–4.91 (m, 2H, $H_{4'}$, $H_{5'}$), 6.06 (m, 1H, $H_{3'}$), 6.21 (m, 1H, $H_{2'}$), 6.47 (d, 1H, $H_{1'}$, $J = 4.0$ Hz), 7.30–7.55 (m, 13H, Ar–H, CH–triazole), 7.88–8.00 (m, 7H, Ar–H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 14.10, 16.33–16.47 ($CH_3$), 22.67, 27.18, 29.34–29.82, 31.91, 48.60 ($CH_2$), 59.50 (CHP), 63.01–63.55 (C5′, $CH_2$), 71.64 (C2′), 75.27 (C3′), 81.28 (C4′), 90.40 (C1′), 118.40, 125.76, 128.53–129.89, 133.46–133.86 (phenyl–CH, triazole–CH), 135.00 (phenyl–C), 149.00 (triazole–C), 165.05–166.04 (CO). ESI-MS (M+H), *m/z* calcd. for $C_{57}H_{75}N_4O_{10}P$: 1007.20, found: 1007.90; HRMS (M+K): calcd. for $C_{57}H_{75}N_4O_{10}PK$: 1045.48524, found: 1045.48309.

*General procedure for the synthesis of diethyl [(4-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)(aryl or alkylamino)-(phenyl)methyl]phosphonates* ***5a–j***

To a solution of 1,2,3-triazole nucleoside analogs **4** (0.45 mmol) in dry methanol (2.5 mL), sodium methoxide (1 equiv.) was added. The reaction mixture was stirred at room temperature until the reaction was complete (30 min). The neutralization was performed with AmberliteIR120 hydrogen form. Afterwards the residue was filtered and evaporated. The crude product was purified by flash silica gel chromatography.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(phenylamino)methyl]phosphonate* ***5a***

Yield: 98%; Rf: 0.30; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.98–1.18 (m, 6H, $-CH_3$), 3.61 (m, 1H, H-5′A), 3.69–3.86 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.93–4.02 (m, 4H, $-OCH_2-$, H-2′,3′), 4.12 (d, 1H, –OH, $J = 5.3$ Hz), 4.40 (t, 1H, –OH, $J = 5.0$ Hz), 4.54 (d, 1H, –OH, $J = 5.3$ Hz), 4.68 (d, 1H, CHP, $J = 24.6$ Hz), 4.95 (br s, 1H, NH), 5.93 (d, 1H, H-1′, $J = 6.3$ Hz), 6.51–6.58 (m, 3H, Ar–H), 6.98 (t, 2H, Ar–H, $J = 7.5$ Hz), 7.30 (m, 2H, Ar–H), 7.42 (d, 2H, Ar–H, $J = 7.5$ Hz), 7.82 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.15–16.41 ($CH_3$), 54.55 (CHP), 61.88–63.79 (C5′, $CH_2$), 70.87 (C2′), 75.99 (C3′), 85.84 (C4′), 92.88 (C1′), 113.95, 118.60, 120.00, 125.86, 128.36–129.52 (phenyl–CH, triazole–CH), 135.79, 146.11–146.73 (phenyl–C, triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{24}H_{31}N_4O_7P$: 518.50, found: 520.00; HRMS (M+K): calcd. for $C_{24}H_{31}N_4O_7PK$: 557.15619, found: 557.15544.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(2-chlorophenylamino)methyl]phosphonate* ***5b***

Yield: 99%; Rf: 0.32; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.08–1.26 (m, 6H, $-CH_3$), 3.57–3.61 (m, 1H, H-5′A), 3.69–3.79 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.84–4.07 (m, 4H, $-OCH_2-$, H-2′,3′), 4.11 (d, 1H, –OH, $J = 5.3$ Hz), 4.38 (t, 1H, –OH, $J = 5.0$ Hz), 4.52 (d, 1H, –OH, $J = 5.3$ Hz), 4.72 (d, 1H, CHP, $J = 24.6$ Hz), 5.24 (br s, 1H, NH), 6.01 (d, 1H, H-1′, $J = 6.3$ Hz), 6.43 (d, 1H, Ar–H, $J = 8.1$ Hz), 6.58 (d, 1H, Ar–H, $J = 6.3$ Hz), 6.93 (t, 1H, Ar–H, $J = 7.2$ Hz), 7.20 (m, 1H, Ar–H), 7.47 (t, 2H, Ar–H, $J = 6.6$ Hz), 7.51 (m, 2H, Ar–H), 7.98 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.01–16.41 ($CH_3$), 54.50 (CHP), 61.85–63.94 (C5′, $CH_2$), 70.90 (C2′), 76.03 (C3′), 85.89 (C4′), 92.95 (C1′), 112.75, 117.63, 118.84, 120.01, 122.39, 125.97, 127.76–128.12, 129.26, 133.73 (phenyl–CH, triazole–CH), 120.09 (C–Cl), 129.73, 135.17, 141.96 (phenyl–C), 146.68 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{24}H_{30}ClN_4O_7P$: 552.94, found: 553.80; HRMS (M+K): calcd. for $C_{24}H_{30}ClN_4O_7PK$: 591.11722, found: 591.11690.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(2-bromophenylamino)methyl]phosphonate* ***5c***

Yield: 98%; Rf: 0.30; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.10–1.20 (m, 6H, $-CH_3$), 3.59–3.62 (m, 1H, H-5′A), 3.71–3.88 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.90–4.06 (m, 4H, $-OCH_2-$, H-2′,3′), 4.11 (d, 1H, –OH, $J = 5.3$ Hz), 4.39 (t, 1H, –OH, $J = 5.0$ Hz), 4.51 (d, 1H, –OH, $J = 5.3$ Hz), 4.76 (d, 1H, CHP, $J = 19.8$ Hz), 5.25 (br s, 1H, NH), 5.78 (d, 1H, H-1′, $J = 6.3$ Hz), 6.34 (d, 1H, Ar–H, $J = 7.2$ Hz), 6.43 (t, 1H, Ar–H, $J = 7.3$ Hz), 6.91 (t, 1H, Ar–H, $J = 7.8$ Hz), 7.19 (m, 3H, Ar–H), 7.47 (m, 2H, Ar–H), 7.65 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.23–16.46 ($CH_3$), 54.77 (CHP), 61.87–64.07 (C5′, $CH_2$), 70.90 (C2′), 76.09 (C3′), 85.95 (C4′), 93.04 (C1′), 110.55 (C–Br), 112.81, 119.36, 119.86, 125.99, 128.17–128.43,

132.52 (phenyl–CH, triazole–CH), 129.74, 135.14, 145.95 (phenyl–C), 146.71 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{24}H_{30}BrN_4O_7P$: 597.40, found: 598.00; HRMS (M+K): calcd. for $C_{24}H_{30}BrN_4O_7PK$: 635.06671, found: 635.06660.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(4-bromophenylamino)methyl]phosphonate* ***5d***
Yield: 99%; Rf: 0.33; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 1.02–1.27 (m, 6H, $-CH_3$), 3.65 (m, 1H, H-5′A), 3.68–3.79 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.84–4.14 (m, 4H, $-OCH_2-$, H-2′,3′), 4.21 (d, 1H, –OH, $J = 5.3$ Hz), 4.48 (t, 1H, –OH, $J = 5.0$ Hz), 4.66 (d, 1H, –OH, $J = 5.3$ Hz), 4.74 (d, 1H, CHP, $J = 25.2$ Hz), 5.25 (br s, 1H, NH), 6.04 (d, 1H, H-1′, $J = 6.2$ Hz), 6.49 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.12 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.37 (d, 2H, Ar–H, $J = 8.0$ Hz), 7.53 (d, 2H, Ar–H, $J = 7.6$ Hz), 8.04 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.15–16.41 ($CH_3$), 56.48 (CHP), 61.91–63.80 (C5′, $CH_2$), 70.86 (C2′), 75.92 (C3′), 85.75 (C4′), 92.82 (C1′), 110.14 (C–Br), 115.54, 120.14, 125.92, 128.38, 131.87 (phenyl–CH, triazole–CH), 129.63, 135.39, 145.47 (phenyl–C), 146.74 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{24}H_{30}BrN_4O_7P$: 597.40, found: 598.10; HRMS (M+K): calcd. for $C_{24}H_{30}BrN_4O_7PK$: 635.06671, found: 635.06616.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(4-fluorophenylamino)methyl]phosphonate* ***5e***
Yield: 95%; Rf: 0.35; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.78–1.18 (m, 6H, $-CH_3$), 3.60 (m, 1H, H-5′A), 3.62–3.87 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.93–4.06 (m, 4H, $-OCH_2-$, H-2′,3′), 4.11 (d, 1H, –OH, $J = 5.3$ Hz), 4.39 (t, 1H, –OH, $J = 5.0$ Hz), 4.55 (d, 1H, –OH, $J = 6.2$ Hz), 4.63 (d, 1H, CHP, $J = 24.6$ Hz), 5.29 (br s, 1H, NH), 5.95 (d, 1H, H-1′, $J = 6.4$ Hz), 6.46 (d, 2H, Ar–H, $J = 8.0$ Hz), 6.66 (d, 2H, Ar–H, $J = 8.1$ Hz), 7.28 (d, 2H, Ar–H, $J = 7.6$ Hz), 7.44 (d, 2H, Ar–H, $J = 7.5$ Hz), 7.93 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.10–16.37 ($CH_3$), 55.14 (CHP), 61.88–63.75 (C5′, $CH_2$), 70.86 (C2′), 75.96 (C3′), 85.80 (C4′), 92.86 (C1′), 114.89–115.78, 120.07, 125.88, 128.39 (phenyl–CH, triazole–CH), 129.60, 135.65, 142.62 (phenyl–C), 146.75 (triazole–C), 154.67 (C–F). ESI-MS (M+H), *m/z* calcd. for $C_{24}H_{30}FN_4O_7P$: 536.49, found: 538.10; HRMS (M+K): calcd. for $C_{24}H_{30}FN_4O_7PK$: 575.14677, found: 575.14637.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(4-chloro-2-methylphenylamino)methyl]-phosphonate* ***5f***
Yield: 98%; Rf: 0.30; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.83–1.02 (m, 6H, $-CH_3$), 1.96 (s, 3H, Ar–$CH_3$), 3.49 (m, 1H, H-5′A), 3.50–3.68 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.71–4.84 (m, 4H, $-OCH_2-$, H-2′,3′), 3.94 (d, 1H, –OH, $J = 5.0$ Hz), 4.12 (t, 1H, –OH, $J = 7.0$ Hz), 4.21 (d, 1H, –OH, $J = 5.0$ Hz), 4.36 (br s, 1H, NH), 4.50 (d, 1H, CHP, $J = 24.6$ Hz), 5.76 (d, 1H, H-1′, $J = 7.6$ Hz), 6.02 (d, 2H, Ar–H, $J = 8.5$ Hz), 6.60 (d, 2H, Ar–H, $J = 7.2$ Hz), 6.73 (s, 1H, Ar–H), 7.13 (d, 2H, Ar–H, $J = 6.6$ Hz), 7.32 (d, 2H, Ar–H, $J = 6.3$ Hz), 7.77 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.29–16.53, 17.45 ($CH_3$), 54.89 (CHP), 62.01–63.85 (C5′, $CH_2$), 70.97 (C2′), 76.09 (C3′), 85.93 (C4′), 92.99 (C1′), 112.58, 120.14, 126.07, 126.65, 128.19, 130.10 (phenyl–CH, triazole–CH), 123.00 (C–Cl), 125.01,129.81, 135.52, 142.91 (phenyl–C), 146.83 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{25}H_{32}ClN_4O_7P$: 566.97, found: 568.10; HRMS (M+K): calcd. for $C_{25}H_{32}ClN_4O_7PK$: 605.13287, found: 605.13238.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(2-naphthalenylamino)methyl]phosphonate* ***5g***
Yield: 98%; Rf: 0.35; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.99–1.38 (m, 6H, $-CH_3$), 3.65 (m, 1H, H-5′A), 3.70–3.86 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.96–4.08 (m, 4H, $-OCH_2-$, H-2′,3′), 4.18 (d, 1H, –OH, $J = 5.4$ Hz), 4.46 (t, 1H, –OH, $J = 5.3$ Hz), 4.61 (d, 1H, –OH, $J = 6.0$ Hz), 4.90 (d, 1H, CHP, $J = 24.0$ Hz), 5.35 (br s, 1H, NH), 5.99 (d, 1H, H-1′, $J = 6.6$ Hz), 6.72 (s, 1H, Ar–H), 7.01 (d, 1H, Ar–H, $J = 8.1$ Hz), 7.10 (t, 1H, Ar–H, $J = 6.9$ Hz), 7.28 (dd, 1H, Ar–H, $J = 7.2$, 2.1 Hz), 7.39–7.56 (m, 7H, Ar–H), 7.86 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.10–16.38 ($CH_3$), 54.46 (CHP), 61.89, 63.54–63.84 (C5′, $CH_2$), 70.84 (C2′), 75.89 (C3′), 85.74 (C4′), 92.79 (C1′), 106.27, 118.16, 120.05, 122.52, 125.83–126.39, 127.54, 128.31, 129.07 (phenyl–CH, triazole–CH), 127.86, 134.68, 135.56, 143.88, 144.06 (phenyl–C), 146.69 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{28}H_{33}N_4O_7P$: 568.56, found: 570.20; HRMS (M+K): calcd. for $C_{28}H_{33}N_4O_7PK$: 607.17184, found: 607.17152.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(benzylamino)methyl]phosphonate* ***5h***
Yield: 95%; Rf: 0.30; Eluent: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.83–1.02 (m, 6H, $-CH_3$), 2.57 (br s, 1H, NH), 3.27 (m, 2H, $-CH_2-$NH–), 3.57 (m, 1H, H-5′A), 3.60–3.71 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.73–3.83 (m, 4H, $-OCH_2-$, H-2′,3′), 3.98 (d, 1H, –OH, $J = 5.0$ Hz), 4.24 (t, 1H, –OH, $J = 4.9$ Hz), 4.38 (d, 1H, –OH, $J = 6.2$ Hz), 4.76 (d, 1H, CHP, $J = 24.6$ Hz), 5.83 (d, 1H, H-1′, $J = 6.3$ Hz), 6.98–7.03 (m, 5H, Ar–H), 7.16 (d, 2H, Ar–H, $J = 6.31$ Hz), 7.45 (d, 7H, Ar–H, $J = 6.3$ Hz), 7.94 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 16.28–16.47 ($CH_3$), 54.28 (CHP), 56.00, 62.50–63.50 (C5′, $CH_2$), 71.00 (C2′), 76.26 (C3′), 84.50 (C4′), 93.22 (C1′), 119.50, 126.03, 127.50, 128.58–130.06 (phenyl–CH, triazole–CH), 135.50, 139.00 (phenyl–C), 147.50 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{25}H_{33}N_4O_7P$: 532.53, found: 534.10; HRMS (M+K): calcd. for $C_{25}H_{33}N_4O_7PK$: 571.17184, found: 571.17077.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(dodecylamino)methyl]phosphonate* ***5i***
Yield: 96%; Rf: 0.34; Eluant: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.92 (m, 6H, $-OCH_2CH_3$, $-CH_3$), 1.15–1.67 (m, 23H, $-CH_2-$, $-OCH_2CH_3$), 7.60 (br s, 1H, NH), 2.33 (m, 2H, $-CH_2-$NH–), 3.52 (m, 1H, H-5′A), 3.83–3.91 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 3.99–4.20 (m, 5H, $-OCH_2-$, H-2′,3′, CHP), 4.31 (d, 1H, –OH, $J = 5.0$ Hz), 4.63 (t, 1H, –OH, $J = 4.9$ Hz), 4.91 (d, 1H, –OH, $J = 6.1$ Hz), 6.12 (d, 1H, H-1′, $J = 6.4$ Hz), 7.28 (d, 2H, Ar–H, $J = 8.2$ Hz), 7.85 (d, 2H, Ar–H, $J = 8.2$ Hz), 8.07 (s, 1H,

CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 14.50, 16.00–16.50 ($CH_3$), 22.65, 27.05, 29.26–40.89 ($CH_2$), 54.50 (CHP), 61.00–61.88 (C5′, $CH_2$), 70.85 (C2′), 75.64 (C3′), 86.48 (C4′), 92.80 (C1′), 121.10, 125.44, 128.41 (phenyl–CH, triazole–CH), 133.00–135.00 (phenyl–C), 147.0 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{30}H_{51}N_4O_7P$: 610.72, found: 611.00.

*Diethyl [(4-(1-(β-D-ribofuranos-1-yl)-1,2,3-triazol-4-yl)-phenyl)(octadecylamino)methyl]phosphonate* ***5j***
Yield: 97%; Rf: 0.36; Eluant: $CH_2Cl_2$/MeOH, 95:5 v/v; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ (ppm): 0.78 (t, 3H, $-CH_3$, $J = 6.9$ Hz), 1.04–1.50 (m, 38H, $-CH_3$, $-CH_2-$), 1.99 (br s, 1H, NH), 2.21 (m, 2H, $-CH_2-$NH–), 3.70 (m, 1H, H-5′A), 3.75–4.15 (m, 4H, $-OCH_2-$, H-5′B, H-4′), 4.20–4.46 (m, 5H, $-OCH_2-$, H-2′,3′, CHP), 4.51 (d, 1H, –OH, $J = 5.0$ Hz), 4.87 (t, 1H, –OH, $J = 5.2$ Hz), 5.29 (d, 1H, –OH, $J = 5.3$ Hz), 5.99 (d, 1H, $H_{1'}$, $J = 4.0$ Hz), 7.34 (d, 2H, Ar–H, $J = 8.4$ Hz), 7.67 (d, 2H, Ar–H, $J = 8.4$ Hz), 8.12 (s, 1H, CH–triazole). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ (ppm): 14.09, 16.00–16.26 ($CH_3$), 22.67, 24.78, 27.08, 29.10–29.69, 31.91, 33.95 ($CH_2$), 54.50 (CHP), 63.00–63.61 (C5′, $CH_2$), 71.50 (C2′), 76.00 (C3′), 86.00 (C4′), 93.00 (C1′), 121.00, 125.44, 128.41 (phenyl–CH, triazole–CH), 133.20–135.10 (phenyl–C), 147.25 (triazole–C). ESI-MS (M+H), *m/z* calcd. for $C_{36}H_{63}N_4O_7P$: 694.88, found: 696.10; HRMS (M+K): calcd. for $C_{36}H_{63}N_4O_7PK$: 733.40660, found: 733.40525.

## Antiviral activity and cytotoxicity assays

The compounds were evaluated against the following viruses: herpes simplex virus type 1 (HSV-1) strain KOS, thymidine kinase-deficient ($TK^-$) HSV-1 KOS strain resistant to ACV ($ACV^r$), herpes simplex virus type 2 (HSV-2) strains Lyons and G, varicella-zoster virus (VZV) strain Oka, $TK^-$ VZV strain 07−1, human cytomegalovirus (HCMV) strains AD-169 and Davis, vaccinia virus Lederle strain, respiratory syncytial virus (RSV) strain Long, vesicular stomatitis virus (VSV), Coxsackie B4, parainfluenza 3, influenza virus A (subtypes H1N1, H3N2), influenza virus B, Reovirus-1, Sindbis, Reovirus-1, Punta Toro, human immunodeficiency virus type 1 strain $III_B$, and human immunodeficiency virus type 2 strain ROD. The antiviral, other than anti-HIV, assays were based on inhibition of virus-induced cytopathicity or plaque formation in human embryonic lung (HEL) fibroblasts, African green monkey cells (Vero), human epithelial cells (HeLa), or Madin–Darby canine kidney cells. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 $CCID_{50}$ of virus (1 $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) or with 20 plaque forming units (PFU) (VZV) in the presence of varying concentrations of the test compounds. Viral cytopathicity or plaque formation was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. Antiviral activity was expressed as the $EC_{50}$ or compound concentration required to reduce virus-induced cytopathogenicity or viral plaque formation by 50%. The methodology of the anti-HIV assays was as follows: human CEM ($\sim 3 \times 10^5$ cells/mL) were infected with 100 $CCID_{50}$ of HIV-1(IIIB) or HIV-2(ROD)/mL and seeded in 200-μL-wells of a microtiter plate containing appropriate dilutions of the test compounds. After 4 days of incubation at 37°C, HIV-induced CEM giant cell formation was examined microscopically.

Cytotoxicity of the test compounds was expressed as the minimum cytotoxic concentration (MCC) or the compound concentration that caused a microscopically detectable alteration of cell morphology. Alternatively, the cytostatic concentration was calculated as the $CC_{50}$, or the compound concentration required reducing cell proliferation by 50% relative to the number of cells in the untreated controls.

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*The authors have declared no conflicts of interest.*

## Dedication

This paper is dedicated to John A. (Jack) Secrist III (University of Alabama) on the occasion of his retirement, in memory of the fruitful scientific collaboration, and for his large contributions to medicinal chemistry.

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