Full Paper

Synthesis of a New Series of Phosphonylated 1,2,3-Triazoles as Acyclic Analogs of Ribavirin

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A novel series of phosphonylated 1,2,3-triazoles as structural acyclic analogs of ribavirin, in which the 1,2,3-triazole ring was substituted at C4′ with COOMe, $CONH_2$, CONHOH, and CH_2NHBoc groups, were synthesized from diethyl azidomethyl-, 2-azidoethyl-, 3-azidopropyl-, 4-azidobutyl-, 2-azido-1-hydroxyethyl-, 3-azido-2-hydroxypropyl-, 2-azidoethoxymethyl- and 2-azidoethoxyethylphosphonate. The efficient synthesis of diethyl azidomethylphosphonate from diethyl 4-nitrobenzenesulfonylmethylphosphonate employing the *in situ* formed azides is described. All synthesized compounds were evaluated *in vitro* for their inhibitory activity against a broad variety of RNA and DNA viruses. No antiviral activity was observed at 100 μM. Only compound **13g** exhibited inhibitory effects on the proliferation of HeLa cells ($IC_{50} = 169 \pm 45$ μM).

Keywords: Antiviral / Azidophosphonates / Cycloaddition / Cytostatic / 1,2,3-Triazoles

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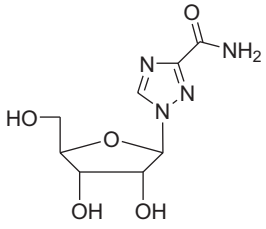
Introduction

The structural features of natural nucleosides have been subjected to various modifications in the search for new therapeutic compounds useful in the treatment of viral diseases. The structural modifications have been performed on both the nucleobase as well as the sugar moieties, although the replacement of natural nucleobases with other heterocyclic residues has been the most common. Ribavirin (virazole; Fig. 1), which exhibits a broad spectrum of antiviral activity against both DNA and RNA viruses, can be considered as the most spectacular example of this approach [1–6]. Structurally ribavirin is a ribofuranosyl nucleoside containing a 1,2,4-triazole-3-carboxamide unit, which is bioisosteric with guanine [7, 8].

For this reason several analogs of ribavirin have been synthesized including 1,2,3-triazole derivatives (Fig. 2), which appeared biologically active [9–13]. For example, compound **1** exhibited specific inhibitory potential against VZV ($EC_{50} = 11$ μM) [9, 10] while **2** displayed moderate activity against HIV-1 ($EC_{50} = 43.8$ μM) [11]. In addition, compound **3** showed antiviral activity against vaccinia virus ($EC_{50} = 0.4$ μM) and cowpox virus ($EC_{50} = 39$ μM) [12] whereas moderate inhibitory effects on the proliferation of human T-lymphocyte cells ($IC_{50} = 36$ μM for Molt4/C8 and $IC_{50} = 73$ μM for CEM) [13] were revealed for **4**.

On the other hand, analogs of acyclovir {9-[(2-hydroxyethoxy)methyl]-9*H*-guanine **5**} containing the 1,2,4-triazole and 1,2,3-triazole rings, compounds **6** and **7a** and **b** (Fig. 3), respectively, have been reported and showed interesting biological activity [14].

Since, in most instances, in order to display antiviral activity nucleosides need to be *in vivo* phosphorylated by cellular kinases to their triphosphates, the synthesis of



Ribavirin

Figure 1. Structure of ribavirin.

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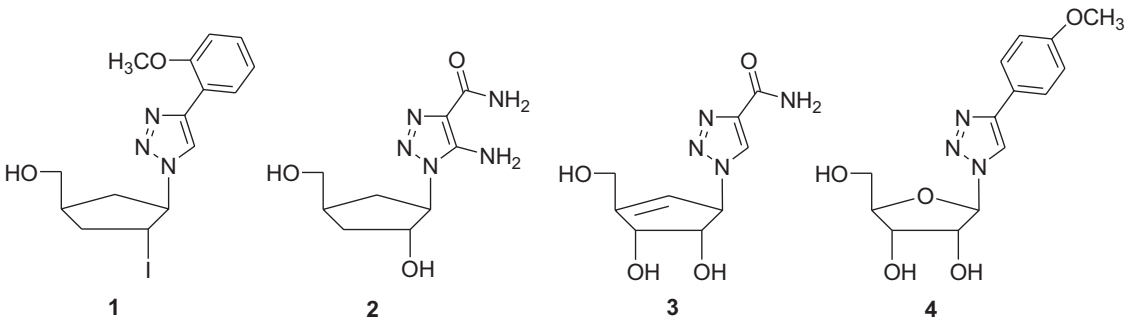


Figure 2. Various analogs of ribavirin.

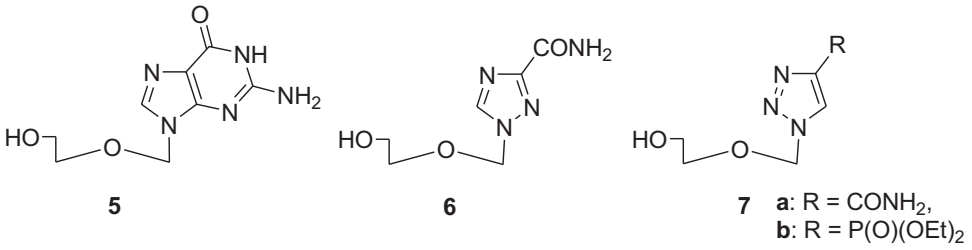


Figure 3. Analogs of acyclovir.

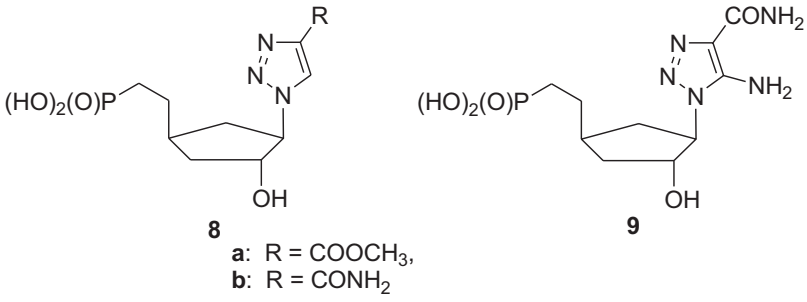


Figure 4. Phosphonate analogs of ribavirin.

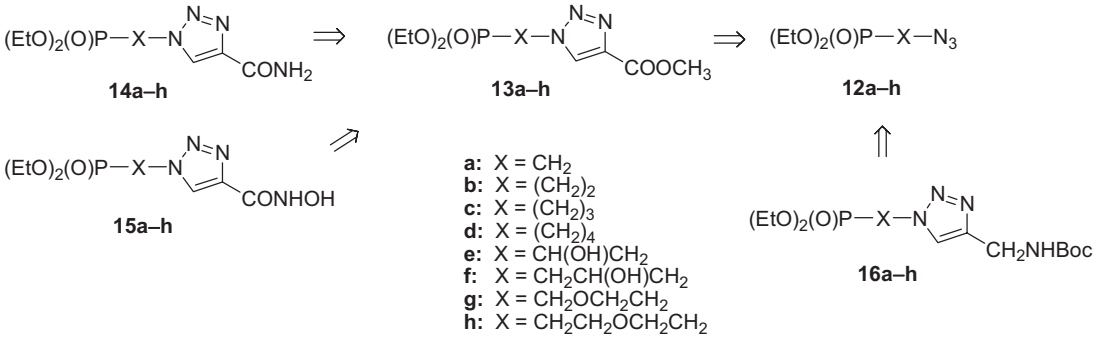
phosphonate analogs of nucleosides with a non-hydrolyzable P–C bond is justified. To this end, Agrofoglio and coworkers [11] synthesized analogs of ribavirin (Fig. 4), which contained a phosphonylmethyl group instead of a phosphate and a cyclopentane ring replacing furanoside and substituted 1,2,3-triazole mimicking 1,2,4-triazole. It appeared that compound **8b** ($R = CONH_2$) displayed moderate activity against HIV-1 ($EC_{50} = 37\ \mu M$) [11].

Furthermore, because the 1,2,3-triazole ring is a component of various classes of compounds displaying antibacterial [15–17], antifungal [18–20], anticancer [21, 22], and antiviral [23–25] activities and it can be efficiently prepared by the Hüisgen cycloaddition [26–37], studies on the design and synthesis of structurally diversified 1,2,3-triazoles with potential biological activity belong to the mainstream of medicinal chemistry [38–49].

In continuation of our involvement in the design of bioactive nucleosides [50–55] the synthesis and biological evaluation of a new series of acyclic phosphonylated 1,2,3-triazoles as structural analogs of ribavirin were performed (Scheme 1). In the projected analogs **14** and **16** a ribofuranosyl moiety of ribavirin was replaced by alkylphosphonate chains; a 1,2,3-triazole ring is supposed to mimic a 1,2,4-triazole, and in addition to a carbamoyl ($CONH_2$) group attached to C3, two new functions, namely a hydroxycarbamoyl (CONHOH) and an aminomethyl (CH_2NH_2), were introduced.

Results and discussion

The starting azidophosphonates **12a** [56–58], **12b** [59–62], **12c** [59, 62], **12d** [63], **12e** [51], **12f** [51], **12g** [55, 64, 65], and **12h** [55] are known and were prepared according to the



Scheme 1. Retrosynthesis of 1,2,3-triazolophosphonates **13** to **16a–h**.

literature methods except for **12a**, since the existing methods for the synthesis of this compound are rather discouraging in terms of application of highly toxic hydrazoic acid [56, 57] and lack of commercial availability of tetramethylguanidinium azide [58]. Our experience with *in situ* generated ammonium azides [50, 51] prompted us to apply this approach also in the synthesis of **12a** via displacement of a nosyl group (Scheme 2). This may be a challenging task, since a nucleophilic substitution at Cα to the phosphorus atom suffers from several limitations [66, 67]. Under our standard conditions (see Scheme 2) diethyl nosyloxymethylphosphonate **11a** was converted quantitatively into **12a** and a crude product could be used in further steps without additional purification.

The 1,2,3-triazoles substituted at C4′ with the methoxycarbonyl group **13a–h** were obtained employing the Hüisgen 1,3-dipolar cycloaddition of the corresponding azidophosphonates **12a–h** and methyl propiolate (Scheme 3). The reactions were carried out at room temperature according to the standard protocol using Cu(I) as a catalyst, which was generated *in situ* from $CuSO_4$ and sodium ascorbate [68–70] to give the corresponding 1,2,3-triazoles **13a–h** in good yields. The products were finally purified by column chromatography on silica gel.

In the same manner, from *N*-(*tert*-butoxycarbonyl)propargylamine and azides **12a–h** the 1,2,3-triazoles **16a–h** were obtained in 1,3-dipolar cycloadditions (Scheme 3). The crude products were efficiently purified by chromatography on silica gel columns.

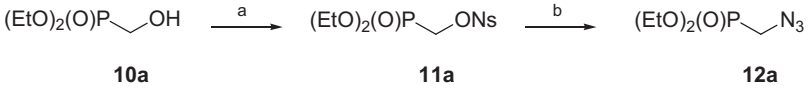
For the preparation of 1,2,3-triazole analogs of ribavirin **14a–h**, the 4-methoxycarbonyl group in **13** was transformed to the 4-carbamoyl group by ammonolysis [71]. The 4-carbamoyl-1,2,3-triazoles **14a–h** were obtained in excellent yields by treating 1,2,3-triazoles **13a–h** with 25% ammonia at room temperature (Scheme 4).

In a similar fashion the 1,2,3-triazoles **13a–h** were also converted to the corresponding hydroxamic acids **15a–h** (Scheme 4). Since phosphonate esters are relatively easily transformed into ammonium salts in the presence of various amines, a modification of the existing procedure [72] relying on performing the reaction of phosphonates **13a–h** with hydroxylamine at 30°C and for 20 min led to the formation of the required products in good yields.

The structures of all new compounds were confirmed on the basis of ^{1}H, ^{31}P, ^{13}C NMR, and IR spectral data as well as by elemental analysis.

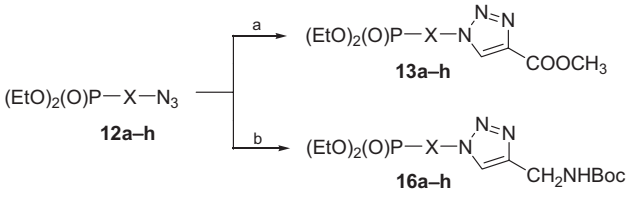
Antiviral activity evaluation

All synthesized compounds were evaluated for their antiviral activities against a wide variety of DNA and RNA viruses using the following cell-based assays: (a) human embryonic lung (HEL) cells: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 (TK^{-} ACV^{r} KOS), varicella-zoster virus, cytomegalovirus, vaccinia virus, and vesicular stomatitis virus; (b) CEM cell cultures: human immunodeficiency virus-1 (HIV-1 and HIV-2); (c) Vero cell cultures: para-influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus; (d) HeLa cell cultures: vesicular stomatitis virus, Coxsackie virus B4 and respiratory syncytial virus; (e) Crandell-Rees Feline Kidney (CRFK) cell cultures: feline corona virus (FIPV), and feline herpes virus (FHV); (f) Madin Darby



Ns: 4-nitrobenzenesulfonyl

Scheme 2. Reagents and conditions: (a) 4-nitrobenzenesulfonyl chloride, Et_3N, CH_2Cl_2, 0–25°C; (b) NaN_3, $(NH_4)_2SO_4$, MeOH, reflux, 4 h.



a. X = CH_2; **b.** X = $(CH_2)_2$; **c.** X = $(CH_2)_3$; **d.** X = $(CH_2)_4$;
e. X = $CH(OH)CH_2$; **f.** X = $CH_2CH(OH)CH_2$;
g. X = $CH_2OCH_2CH_2$; **h.** X = $CH_2CH_2OCH_2CH_2$

Scheme 3. Reagents and conditions: (a) $HCCCOOCH_3$ (1 equiv.), $CuSO_4 \cdot 5H_2O$ (0.05 equiv.), sodium ascorbate (0.1 equiv.), H_2O–*t*-BuOH (2:1), r.t., 12 h; (b) $HCCCH_2NHBoc$ (1 equiv.), $CuSO_4 \cdot 5H_2O$ (0.05 equiv.), sodium ascorbate (0.1 equiv.), H_2O–*t*-BuOH (2:1), r.t., 12 h.

Canine Kidney (MDCK) cell cultures: influenza A virus H1N1 subtype (A/PR/8), influenza A virus H3N2 subtype (A/HK/7/87), and influenza B virus (B/HK/5/72). Ganciclovir, cidofovir, acyclovir, brivudin, (*S*)-9-(2,3-dihydroxypropyl)adenine [(*S*)-DHPA], *Hippeastrum* hybrid agglutinin (HHA), *Urtica dioica* agglutinin (UDA), dextran sulfate (molecular weight 5000, DS-5000), ribavirin, oseltamivir carboxylate, amantadine, and rimantadine were used as the reference compounds. The antiviral activity was expressed as the EC_{50}: the compound concentration required to reduce virus plaque formation (VZV) by 50% or to reduce virus-induced cytopathogenicity by 50% (other viruses). None of the compounds were inhibitory against the different viruses at 100 μM.

Evaluation of cytotoxicity and cytostatic activity

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. None of the tested compounds affected the cell morphology of Vero, HEL and HeLa cells (MCC or CC_{50}) at compound concentrations up to 100 μM. The cytostatic activity of the tested compounds was defined as the 50% cytostatic inhibitory concentration (IC_{50}). Only compound **13g** inhibited the proliferation of HeLa cells ($IC_{50} = 169 \pm 45$ μM).

Conclusion

Safe and efficient synthesis of diethyl azidomethylphosphonate from diethyl 4-nitrobenzenesulfonylmethylphosphonate was elaborated using sodium azide in the presence of ammonium sulfate.

The diethyl azidomethyl-, 2-azidoethyl-, 3-azidopropyl-, 4-azidobutyl-, 2-azido-1-hydroxyethyl-, 3-azido-2-hydroxypropyl-, 2-azidoethoxymethyl- and 2-azidoethoxyethylphosphonates were transformed into the corresponding 1,2,3-triazoles substituted at C4′ with methoxycarbonyl, carbamoyl, *N*-(*tert*-butoxycarbonyl)aminomethyl and hydroxycarbamoyl groups to obtain structural analogs of ribavirin.

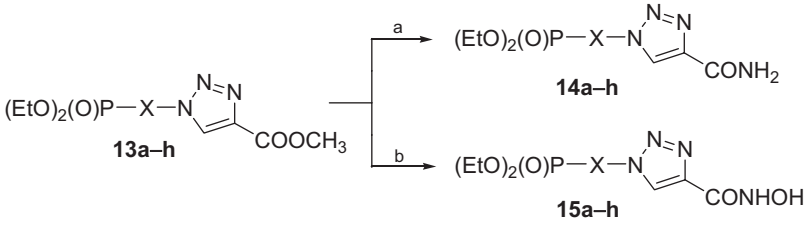
All synthesized compounds were tested for their antiviral activities against DNA and RNA viruses but were found inactive. Phosphonate **13g** exhibited inhibitory effect on the proliferation of HeLa cells ($IC_{50} = 169 \pm 45$ μM).

Experimental

^1H NMR spectra were taken in $CDCl_3$ or CD_3OD on the following spectrometers: Varian Mercury-300 with TMS as an internal standard; chemical shifts δ in ppm with respect to TMS; coupling constants J in Hz. ^{13}C NMR spectra were recorded for $CDCl_3$ or CD_3OD solutions on a Varian Mercury-300 spectrometer at 75.5. ^{31}P NMR spectra were taken in $CDCl_3$ or CD_3OD on a Varian Mercury-300 at 121.5 MHz.

IR spectral data were measured on an Infinity MI-60 FT-IR spectrometer. Melting points were determined on a Boetius apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of this faculty on a Perkin Elmer PE 2400 CHNS analyzer.

The following adsorbents were used: column chromatography, Merck silica gel 60 (70–230 mesh); analytical TLC, Merck TLC plastic sheets silica gel 60 F_{254}. TLC plates were developed in



a. X = CH_2; **b.** X = $(CH_2)_2$; **c.** X = $(CH_2)_3$; **d.** X = $(CH_2)_4$;
e. X = $CH(OH)CH_2$; **f.** X = $CH_2CH(OH)CH_2$;
g. X = $CH_2OCH_2CH_2$; **h.** X = $CH_2CH_2OCH_2CH_2$

Scheme 4. Reagents and conditions: (a) 25% ammonia, MeOH, r.t., 4 h; (b) 50% aq. hydroxylamine, EtOH, 30°C, 20 min.

chloroform–methanol solvent systems. Visualization of spots was effected with iodine vapors. All solvents were purified by methods described in the literature.

*Synthesis of diethyl azidomethylphosphonate **12a** [56–58]*

A mixture of the nosyl derivative **11** (3.265 g, 9.539 mmol), sodium azide (1.489 g, 22.89 mmol) and ammonium sulfate (2.268 g, 17.17 mmol) in methanol (20 mL) was stirred at 65°C for 4 h. After evaporation of solvents the residue was suspended in ethyl acetate (10 mL) and filtered through a layer of Celite. The solution was concentrated *in vacuo* to give pure diethyl azidomethylphosphonate **12a** (1.743 g, 94%) as a colorless oil. IR (film): $\nu = 2888, 2872, 2189, 1225, 1028\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.27–4.17$ (m, 4H, $2 \times POCH_2CH_3$); 3.46 (d, $J = 11.8$ Hz, 2H, PCH_2); 1.41 (t, $J = 6.9$ Hz, 3H, $POCH_2CH_3$); 1.40 (t, $J = 6.9$ Hz, 3H, $POCH_2CH_3$); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.97$ ppm.

General procedure for copper-catalyzed cycloaddition reaction

To a solution of azidophosphonate **12** (1.00 mmol) in *t*-BuOH (0.5 mL) and H_2O (1 mL) were added $CuSO_4 \cdot 5H_2O$ (0.10 mmol), sodium ascorbate (0.20 mmol), and methyl propiolate or *N*-(*tert*-butoxycarbonyl)propargylamine (1.00 mmol). This suspension was stirred vigorously at room temperature for 12 h. After removal of solvents the residue was suspended in chloroform (5 mL) and filtered through a layer of Celite. The solution was concentrated *in vacuo* and the crude product was purified on a silica gel column with chloroform–methanol mixtures (20:1 or 10:1 v/v) to give the desired 1,2,3-triazoles **13a–h** or **16a–h**.

*Diethyl [4-(methoxycarbonyl)-1,2,3-triazol-1-yl]-methylphosphonate **13a***

The compound **13a** was prepared from azidomethylphosphonate **12a** (0.200 g, 1.04 mmol) and methyl propiolate (0.087 g, 1.04 mmol) according to the general procedure. The product was purified on a silica gel column (chloroform–methanol 100:1 v/v) to afford phosphonate **13a** as a colorless oil (0.225 g, 79%). IR (film): $\nu = 3273, 2988, 2952, 1731, 1239, 1038\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.33$ (d, $J = 1.1$ Hz, 1H, HC5′); 4.82 (d, $J = 13.3$ Hz, 2H, PCH_2); 4.20–4.10 (m, 4H, $2 \times POCH_2CH_3$), 3.97 (s, 3H, $COOCH_3$); 1.31 (t, $J = 7.0$ Hz, 3H, $POCH_2CH_3$); 1.30 (t, $J = 7.0$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.7$ (s, C=O); 140.2 (s, HC=C); 128.5 (s, HC=C); 63.8 (d, $J = 6.6$ Hz, POC); 52.4 (s, $COOCH_3$); 46.1 (d, $J = 154.6$ Hz, PC); 16.5 (d, $J = 5.7$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 16.02$ ppm. Anal. calcd. for $C_9H_{16}N_3O_5P$: C, 38.99; H, 5.82; N, 15.16. Found: C, 39.12; H, 5.71; N, 15.03.

*Diethyl 2-[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]-ethylphosphonate **13b***

The compound **13b** was prepared from azidophosphonate **12b** (0.300 g, 1.45 mmol) and methyl propiolate (0.122 g, 1.45 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) affording phosphonate **13b** as a colorless oil (0.468 g, 82%). IR (film): $\nu = 2988, 1733, 1228, 1045\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (s, 1H, HC5′); 4.70 (dt, $J = 13.6$ Hz, $J = 7.7$ Hz, 2H, PCH_2CH_2); 4.15–4.05 (m, 4H, $2 \times POCH_2CH_3$), 3.96 (s, 3H, $COOCH_3$); 2.45 (dt, $J = 18.5$ Hz, $J = 7.7$ Hz, 2H, PCH_2); 1.31 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); 1.30 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.9$ (s, C=O); 139.7 (s, HC=C); 128.1 (s, HC=C); 62.3 (d, $J = 6.5$ Hz, POC); 52.3 (s, $COOCH_3$); 45.1 (d, $J = 2.0$ Hz, PC*C*); 27.1 (d, $J = 141.7$ Hz, PC); 16.5 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.15$ ppm. Anal. calcd. for $C_{10}H_{18}N_3O_5P$: C, 41.24; H, 6.23; N, 14.43. Found: C, 41.06; H, 6.31; N, 14.38.

*Diethyl 3-[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]-propylphosphonate **13c***

The compound **13c** was prepared from azidophosphonate **12c** (0.350 g, 1.58 mmol) and methyl propiolate (0.132 g, 1.58 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to give phosphonate **13c** as a colorless oil (0.483 g, 97%). IR (film): $\nu = 2985, 2910, 1731, 1230, 1048\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.17$ (s, 1H, HC5′); 4.55 (t, $J = 6.9$ Hz, 2H, $PCH_2CH_2CH_2$); 4.17–4.04 (m, 4H, $2 \times POCH_2CH_3$), 3.96 (s, 3H, $COOCH_3$); 2.28 (dqu, $J = 15.3$ Hz, $J = 6.9$ Hz, 2H, PCH_2CH_2); 1.72 (ddd, $J = 15.3$ Hz, $J = 10.8$ Hz, $J = 6.9$ Hz, 2H, PCH_2); 1.33 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.8$ (s, C=O); 139.5 (s, HC=C); 127.9 (s, HC=C); 61.8 (d, $J = 6.3$ Hz, POC); 52.0 (s, $COOCH_3$); 50.1 (d, $J = 14.9$ Hz, PC*C*), 23.5 (d, $J = 4.7$ Hz, PC*C*); 22.2 (d, $J = 142.8$ Hz, PC); 16.4 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.63$ ppm. Anal. calcd. for $C_{11}H_{20}N_3O_5P$: C, 43.28; H, 6.60; N, 13.77. Found: C, 42.98; H, 6.55; N, 13.73.

*Diethyl 4-[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]-butylphosphonate **13d***

The compound **13d** was prepared from azidophosphonate **12d** (0.350 g, 1.49 mmol) and methyl propiolate (0.124 g, 1.49 mmol) according to the general procedure. The product was purified on a silica gel column (chloroform–methanol 100:1 v/v) to give phosphonate **13d** as a colorless oil (0.304 g, 81%). IR (film): $\nu = 2987, 2900, 1731, 1215, 1031\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.10$ (s, 1H, HC5′); 4.44 (t, $J = 7.2$ Hz, 2H, $PCH_2CH_2CH_2CH_2$); 4.15–4.02 (m, 4H, $2 \times POCH_2CH_3$), 3.96 (s, 3H, $COOCH_3$); 2.13–2.03 (m, 2H, CH_2); 1.83–1.77 (m, 4H, $2 \times CH_2$); 1.32 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.8$ (s, C=O); 139.4 (s, HC=C); 127.5 (s, HC=C); 61.4 (d, $J = 6.6$ Hz, POC); 51.9 (s, $COOCH_3$); 49.8 (s, PC*CCC*); 30.4 (d, $J = 15.2$ Hz, PC*CC*), 24.6 (d, $J = 141.4$ Hz, PC); 19.4 (d, $J = 5.2$ Hz, PC*C*); 16.3 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 31.77$ ppm. Anal. calcd. for $C_{12}H_{22}N_3O_5P$: C, 45.14; H, 6.94; N, 13.16. Found: C, 45.24; H, 7.05; N, 13.13.

*Diethyl 1-hydroxy-2-[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]ethylphosphonate **13e***

The compound **13e** was prepared from azidophosphonate **12e** (0.200 g, 0.896 mmol) and methyl propiolate (0.074 g, 0.896 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to give phosphonate **13e** as white needles (0.249 g, 91%). m.p.: 118–120°C; IR (KBr): $\nu = 3270, 2989, 2911, 1732, 1219, 1045\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.34$ (s, 1H, HC5′); 5.40 (brs, 1H, OH); 4.88 (ddd, $J = 14.2$ Hz, $J = 5.0$ Hz, $J = 2.7$ Hz, 1H, $PCCH_aH_b$); 4.51 (ddd, $J = 14.2$ Hz, $J = 10.0$ Hz, $J = 5.6$ Hz, 1H, $PCCH_aH_b$); 4.35–4.30 (m, 1H, PC*H*(OH)), 4.26–4.13 (m, 4H, $2 \times POCH_2CH_3$), 3.95 (s, 3H, $COOCH_3$); 1.35 (t, $J = 7.2$ Hz, 3H,

$POCH_2CH_3$); 1.34 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.9$ (s, C=O); 139.3 (s, HC=C); 129.5 (s, HC=C); 66.7 (d, $J = 165.5$ Hz, PC); 63.7 (d, $J = 7.2$ Hz, POC); 52.2 (s, $COOCH_3$); 51.9 (d, $J = 9.7$ Hz, PC*C*); 16.6 (d, $J = 5.1$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.91$ ppm. Anal. calcd. for $C_{10}H_{18}N_3O_6P$: C, 39.09; H, 5.91; N, 13.68. Found: C, 39.21; H, 5.84; N, 13.58.

Diethyl 2-hydroxy-3-[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]propylphosphonate ***13f***

The compound **13f** was prepared from azidophosphonate **12f** (0.500 g, 2.11 mmol) and methyl propiolate (0.177 g, 2.11 mmol) according to the general procedure. The product was purified on a silica gel column (chloroform–methanol 100:1 v/v) to afford phosphonate **13f** as a white solid (0.666 g, 98%). m.p.: 104–106°C; IR (KBr): $\nu = 3308$, 2989, 2955, 1733, 1221, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.33$ (s, 1H, HC5′); 4.64–4.53 (m, 1H, PCCCH_aH_b); 4.51–4.36 (m, 3H, PCCHCH_aH_b, OH); 4.21–4.05 (m, 4H, $2 \times POCH_2CH_3$), 3.96 (s, 3H, $COOCH_3$); 2.02 (ddd, $J = 19.6$ Hz, $J = 15.2$ Hz, $J = 3.0$ Hz, 1H, PCH_aH_b); 1.76 (ddd, $J = 16.6$ Hz, $J = 15.2$ Hz, $J = 9.6$ Hz, 1H, PCH_aH_b); 1.35 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); 1.27 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 161.0$ (s, C=O); 139.5 (s, HC=C); 129.3 (s, HC=C); 65.2 (d, $J = 3.7$ Hz, PC*C*); 62.4 (d, $J = 6.4$ Hz, POC); 62.3 (d, $J = 6.4$ Hz, POC); 56.2 (d, $J = 17.2$ Hz, PC*C*C); 52.2 (s, $COOCH_3$); 30.8 (d, $J = 140.4$ Hz, PC); 16.5 (d, $J = 5.3$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.24$ ppm. Anal. calcd. for $C_{11}H_{20}N_3O_6P$: C, 41.12; H, 6.27; N, 13.08. Found: C, 41.28; H, 6.36; N, 12.93.

Diethyl 2-{[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]ethoxy}-methylphosphonate ***13g***

The compound **13g** was prepared from azidophosphonate **12g** (0.300 g, 1.26 mmol) and methyl propiolate (0.105 g, 1.26 mmol) according to the general procedure. The product was purified on a silica gel column (chloroform–methanol 100:1 v/v) to give phosphonate **13g** as a colorless oil (0.338 g, 83%). IR (film): $\nu = 3139$, 2988, 2909, 1731, 1215, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.30$ (s, 1H, HC5′); 4.64 (t, $J = 4.7$ Hz, 2H, OCH_2CH_2N); 4.18–4.08 (m, 4H, $2 \times POCH_2CH_3$), 4.00 (t, $J = 4.7$ Hz, 2H, OCH_2CH_2N); 3.95 (s, 3H, $COOCH_3$); 3.79 (d, $J = 8.2$ Hz, 2H, PCH_2O); 1.32 (t, $J = 7.1$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 161.0$ (s, C=O); 139.8 (s, HC=C); 128.8 (s, HC=C); 70.9 (d, $J = 10.5$ Hz, OCH_2CH_2N); 65.3 (d, $J = 166.7$ Hz, PC); 62.7 (d, $J = 6.5$ Hz, POC); 52.3 (s, $COOCH_3$); 50.5 (s, OCH_2CH_2N); 16.7 (d, $J = 6.2$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.30$ ppm. Anal. calcd. for $C_{11}H_{20}N_3O_6P$: C, 41.12; H, 6.27; N, 13.08. Found: C, 41.00; H, 6.35; N, 13.11.

Diethyl 2-{[4-(methoxycarbonyl)-1,2,3-triazol-1-yl]ethoxy}-ethylphosphonate ***13h***

The compound **13h** was prepared from azidophosphonate **12h** (0.320 g, 1.27 mmol) and methyl propiolate (0.107 g, 1.27 mmol) according to the general procedure. The product was purified by chromatography on a silica gel column (chloroform–methanol 100:1 v/v) to afford phosphonate **13h** as a colorless oil (0.340 g, 80%). IR (film): $\nu = 3141$, 2987, 2908, 1733, 1231, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.30$ (s, 1H, HC5′); 4.60 (t, $J = 5.0$ Hz, 2H, OCH_2CH_2N); 4.15–4.04 (m, 4H, $2 \times POCH_2CH_3$), 3.96 (s, 3H, $COOCH_3$); 3.83 (t, $J = 5.0$ Hz, 2H, OCH_2CH_2N); 3.70 (dt, $J = 13.1$ Hz, $J = 7.2$ Hz, 2H, PCH_2CH_2O); 2.07 (dt, $J = 18.6$ Hz, $J = 7.2$ Hz, 2H, PCH_2CH_2O); 1.31 (t, $J = 7.0$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 161.0$ (s, C=O); 139.7 (s, HC=C); 128.7 (s, HC=C); 68.6 (s, OCH_2CH_2N); 65.3 (d, $J = 1.9$ Hz, PCH_2CH_2O); 61.8 (d, $J = 6.5$ Hz, POC); 52.2 (s, $COOCH_3$); 50.6 (s, OCH_2CH_2N); 26.9 (d, $J = 140.5$ Hz, PC); 16.5 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 28.86$ ppm. Anal. calcd. for $C_{12}H_{22}N_3O_6P$: C, 42.99; H, 6.61; N, 12.53. Found: C, 43.10; H, 6.73; N, 12.71.

Diethyl 4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]methylphosphonate ***16a***

The compound **16a** was prepared from azidomethylphosphonate **12a** (0.150 g, 0.777 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.121 g, 0.777 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to afford phosphonate **16a** as a colorless oil (0.214 g, 89%). IR (film): $\nu = 3310$, 2982, 2935, 1704, 1250, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (s, 1H, HC5′); 5.10 (brs, 1H, NH); 4.74 (d, $J = 13.1$ Hz, 2H, PCH_2); 4.40 (d, $J = 6.0$ Hz, 2H, CH_2); 4.17–4.07 (m, 4H, $2 \times POCH_2CH_3$), 1.43 (s, 9H, $3 \times CH_3$); 1.30 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.7$ (s, C=O); 145.9 (s, HC=C); 122.9 (s, HC=C); 79.5; 63.4 (d, $J = 6.6$ Hz, POC); 45.8 (d, $J = 154.9$ Hz, PC); 36.1; 28.4; 16.4 (d, $J = 5.4$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 16.90$ ppm. Anal. calcd. for $C_{13}H_{25}N_4O_5P$: C, 44.82; H, 7.23; N, 16.08. Found: C, 44.69; H, 7.12; N, 16.13.

Diethyl 2-{4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]}ethylphosphonate ***16b***

The compound **16b** was prepared from azidophosphonate **12b** (0.166 g, 0.801 mmol) and *N*-(*tert*-butoxycarbonyl)propargyl amine (0.124 g, 0.801 mmol) according to the general procedure. The product was purified by chromatography on a silica gel column (chloroform–methanol 100:1 v/v) to give phosphonate **16b** as a colorless oil (0.226 g, 78%). IR (film): $\nu = 3322$, 2982, 2934, 1706, 1249, 1028 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (s, 1H, HC5′); 5.12 (brs, 1H, NH); 4.59 (dt, $J = 11.4$ Hz, $J = 7.8$ Hz, 2H, PCCH_2); 4.39 (d, $J = 7.8$ Hz, 2H, CH_2); 4.15–4.05 (m, 4H, $2 \times POCH_2CH_3$), 2.41 (dt, $J = 18.3$ Hz, $J = 7.8$ Hz, 2H, PCH_2); 1.49 (s, 9H, $3 \times CH_3$); 1.32 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 156.0$ (s, C=O); 145.5 (s, HC=C); 122.3 (s, HC=C); 79.5; 62.2 (d, $J = 6.6$ Hz, POC); 44.5; 36.0; 28.4; 27.2 (d, $J = 140.9$ Hz, PC); 16.4 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.58$ ppm. Anal. calcd. for $C_{14}H_{27}N_4O_5P$: C, 46.40; H, 7.51; N, 15.46. Found: C, 46.33; H, 7.68; N, 15.17.

Diethyl 3-{4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]}propylphosphonate ***16c***

The compound **16c** was prepared from azidophosphonate **12c** (0.165 g, 0.746 mmol) and *N*-(*tert*-butoxycarbonyl)propargyl amine (0.116 g, 0.746 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to afford phosphonate **16c** as a colorless oil (0.199 g, 78%). IR (film): $\nu = 3297$, 2981, 2935, 1706, 1249, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (s, 1H, HC5′); 5.12 (brs, 1H, NH); 4.44 (t, $J = 7.5$ Hz, 2H, PCCCH_2); 4.39 (d, $J = 5.7$ Hz, 2H); 4.19–4.01 (m, 4H, $2 \times POCH_2CH_3$), 2.22 (dqu, $J = 15.3$ Hz, $J = 7.5$ Hz, 2H, PCCH_2); 1.72 (ddd, $J = 15.3$ Hz, $J = 9.3$ Hz, $J = 7.5$ Hz, 2H, PCH_2); 1.45 (s, 9H, $3 \times CH_3$); 1.33 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.7$

(s, C=O); 145.4 (s, HC=C); 122.1 (s, HC=C); 79.2; 61.7 (d, $J = 6.3$ Hz, POC); 49.8 (d, $J = 16.1$ Hz, PCCC), 35.9; 28.3; 23.5 (d, $J = 4.9$ Hz, PCC); 22.4 (d, $J = 142.6$ Hz, PC); 16.4 (d, $J = 6.0$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.32$ ppm. Anal. calcd. for $C_{15}H_{29}N_4O_5P$: C, 47.87; H, 7.77; N, 14.89. Found: C, 47.72; H, 7.65; N, 15.00.

Diethyl 4-{4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]}butylphosphonate **16d**

The compound **16d** was prepared from azidophosphonate **12d** (0.161 g, 0.684 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.106 g, 0.684 mmol) according to the general procedure. The product was purified by chromatography on a silica gel column (chloroform–methanol 100:1 v/v) to give phosphonate **16d** as a colorless oil (0.219 g, 82%). IR (film): $\nu = 3308$, 2982, 2926, 1707, 1245, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (s, 1H, HC5′); 5.14 (brs, 1H, NH); 4.40–4.33 (m, 4H, PCCCCH_2, CH_2NHBoc); 4.16–4.02 (m, 4H, 2 × POCH_2CH$_3$), 2.03 (qv, 2H, $J = 7.5$ Hz, PCCCH_2); 1.84–1.75 (m, 4H, PCH_2CH_2); 1.44 (s, 9H, 3 × CH$_3$); 1.32 (t, $J = 7.2$ Hz, 6H, 2 × POCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.9$ (s, C=O); 140.0 (s, HC=C); 121.9 (s, HC=C); 79.7; 61.4 (d, $J = 6.5$ Hz, POC); 50.0 (s, PCCCC); 36.3; 30.9 (d, $J = 15.3$ Hz, PCCC), 28.6; 25.1 (d, $J = 139.7$ Hz, PC); 19.8 (d, $J = 5.1$ Hz, PCC); 16.6 (d, $J = 6.0$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 32.02$ ppm. Anal. calcd. for $C_{16}H_{31}N_4O_5P$: C, 49.22; H, 8.00; N, 14.59. Found: C, 49.12; H, 7.71; N, 14.93.

Diethyl 2-{4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]}-1-hydroxyethylphosphonate **16e**

The compound **16e** was prepared from azidophosphonate **12e** (0.131 g, 0.586 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.091 g, 0.586 mmol) according to the general procedure. The phosphonate **16e** (0.147 g, 76%) was obtained as a white solid after purification on a silica gel with chloroform–methanol (100:1 v/v) and crystallization from ethyl acetate–hexane. m.p.: 102–104°C; IR (KBr): $\nu = 3309$, 2982, 2934, 1705, 1250, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$ (s, 1H, HC5′); 5.34 (brs, 1H, NH); 4.80 (ddd, $J = 14.4$ Hz, $J = 5.4$ Hz, $J = 2.4$ Hz, 1H, PCCH_aH$_b$); 4.60 (ddd, $J = 14.4$ Hz, $J = 9.3$ Hz, $J = 5.1$ Hz, 1H, PCCH$_a$$H_b$); 4.35 (d, $J = 6.0$ Hz, 2H); 4.35–4.30 (m, 1H, PCH(OH)); 4.29–4.13 (m, 4H, 2 × POCH_2CH$_3$); 1.43 (s, 9H, 3 × CH$_3$); 1.36 (t, $J = 7.2$ Hz, 3H, POCH$_2$CH_3); 1.35 (t, $J = 7.2$ Hz, 3H, POCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.8$ (s, C=O); 145.0 (s, HC=C); 123.8 (s, HC=C); 79.5; 66.9 (d, $J = 164.3$ Hz, PC); 63.5 (d, $J = 7.4$ Hz, POC); 63.4 (d, $J = 7.4$ Hz, POC); 51.7 (d, $J = 10.0$ Hz, C-2); 36.0; 28.5; 16.6 (d, $J = 5.4$ Hz, POCC); 16.5 (d, $J = 5.4$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.26$ ppm. Anal. calcd. for $C_{14}H_{27}N_4O_6P$: C, 44.44; H, 7.19; N, 14.81. Found: C, 44.22; H, 7.06; N, 14.73.

Diethyl 3-{4-[(N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]}-2-hydroxypropylphosphonate **16f**

The compound **16f** was prepared from azidophosphonate **12f** (0.163 g, 0.687 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.107 g, 0.687 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to afford phosphonate **16f** as a colorless oil (0.224 g, 83%). IR (film): $\nu = 3328$, 2982, 2913, 1703, 1249, 1029 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H, HC5′); 5.27 (brs, 1H, NH); 4.57–4.49 (m, 1H, PCCCH_aH$_b$); 4.45–4.34 (m, 5H, PCCCH$_a$$H_b$, PCC$H$(O$H$), C$H_2$NHBoc); 4.19–4.04 (m, 4H, 2 × POCH_2CH$_3$), 1.99 (ddd, $J = 19.2$ Hz, $J = 15.2$ Hz, $J = 3.3$ Hz, 1H, PCH_aH$_b$); 1.84 (ddd, $J = 17.1$ Hz, $J = 15.2$ Hz, $J = 9.0$ Hz, 1H, PCH$_a$$H_b$); 1.44 (s, 9H, 3 × CH$_3$); 1.34 (t, $J = 7.2$ Hz, 3H, POCH$_2$CH_3); 1.32 (t, $J = 7.2$ Hz, 3H, POCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 156.0$ (s, C=O); 145.3 (s, HC=C); 123.6 (s, HC=C); 79.6; 65.5 (d, $J = 3.4$ Hz, PCC); 62.4 (d, $J = 6.3$ Hz, POC); 62.3 (d, $J = 6.3$ Hz, POC); 56.0 (d, $J = 16.6$ Hz, PCCC); 30.9 (d, $J = 140.3$ Hz, PC); 28.3; 16.6 (d, $J = 6.0$ Hz, POCC); 16.5 (d, $J = 6.0$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.47$ ppm. Anal. calcd. for $C_{15}H_{29}N_4O_6P$: C, 45.91; H, 7.45; N, 14.28. Found: C, 46.10; H, 7.51; N, 14.13.

Diethyl 2-{[4-N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]methoxy}ethylphosphonate **16g**

The compound **16g** was prepared from azidophosphonate **12g** (0.145 g, 0.611 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.095 g, 0.611 mmol) according to the general procedure. The product was purified by column chromatography on silica gel (chloroform–methanol 100:1 v/v) to afford phosphonate **16g** as a colorless oil (0.192 g, 80%). IR (film): $\nu = 3313$, 2981, 2932, 1708, 1252, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (s, 1H, HC5′); 5.16 (brs, 1H, NH); 4.55 (t, $J = 5.1$ Hz, 2H, OCH$_2$CH_2N); 4.40 (d, $J = 6.0$ Hz, 2H, CH_2NHBoc); 4.17–4.08 (m, 4H, 2 × POCH_2CH$_3$), 3.98 (t, $J = 5.1$ Hz, 2H, OCH_2CH$_2$N); 3.77 (d, $J = 7.8$ Hz, 2H, PCH$_2$O); 1.44 (s, 9H, 3 × CH$_3$); 1.32 (t, $J = 7.2$ Hz, 6H, 2 × POCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.8$ (s, C=O); 145.3 (s, HC=C); 123.0 (s, HC=C); 79.6; 71.4 (d, $J = 10.3$ Hz, OCH$_2$CH$_2$N); 65.3 (d, $J = 166.3$ Hz, PC); 62.6 (d, $J = 6.6$ Hz, POC); 50.2 (s, OCH$_2$CH_2N); 36.3; 28.5; 16.6 (d, $J = 5.4$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 20.72$ ppm. Anal. calcd. for $C_{15}H_{29}N_4O_6P$: C, 45.91; H, 7.45; N, 14.28. Found: C, 45.87; H, 7.41; N, 14.18.

Diethyl 2-{[4-N-tert-butoxycarbonyl)aminomethyl-1,2,3-triazol-1-yl]ethoxy}ethylphosphonate **16h**

The compound **16h** was prepared from azidophosphonate **12h** (0.163 g, 0.649 mmol) and *N*-(*tert*-butoxycarbonyl)propargylamine (0.101 g, 0.649 mmol) according to the general procedure. The product was purified by chromatography on a silica gel column (chloroform–methanol 100:1 v/v) to give phosphonate **16h** as a colorless oil (0.264 g, 86%). IR (film): $\nu = 3317$, 2980, 2933, 1704, 1250, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.71$ (s, 1H, HC5′); 5.31 (brs, 1H, NH); 4.52 (t, $J = 4.8$ Hz, 2H, OCH$_2$CH_2N); 4.40 (d, $J = 5.4$ Hz, 2H, CH_2NHBoc); 4.14–4.01 (m, 4H, 2 × POCH_2CH$_3$), 3.81 (t, $J = 4.8$ Hz, 2H, OCH_2CH$_2$N); 3.69 (dt, $J = 13.8$ Hz, $J = 7.2$ Hz, 2H, PCH$_2$CH_2O); 2.06 (dt, $J = 18.6$ Hz, $J = 7.2$ Hz, 2H, PCH_2CH$_2$O); 1.45 (s, 9H, 3 × CH$_3$); 1.31 (t, $J = 7.2$ Hz, 6H, 2 × POCH$_2$CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 155.7$ (s, C=O); 145.1 (s, HC=C); 123.0 (s, HC=C); 79.2; 68.9 (s, OCH_2CH$_2$N); 65.0 (d, $J = 2.0$ Hz, PCH$_2$CH_2O); 61.6 (d, $J = 6.6$ Hz, POC); 50.0 (s, OCH$_2$CH$_2$N); 36.1; 28.3; 26.7 (d, $J = 140.6$ Hz, PC); 16.4 (d, $J = 6.0$ Hz, POCC); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.06$ ppm. Anal. calcd. for $C_{16}H_{31}N_4O_6P$: C, 47.28; H, 7.69; N, 13.79. Found: C, 47.19; H, 7.71; N, 13.90.

General procedure for synthesis of 1,2,3-triazoles **14a–h**

A solution of diethyl [4-(methoxycarbonyl)-1,2,3-triazol-1-yl]alkylphosphonates **13a–h** (1.0 mmol) in methanol (3 mL) containing 25% ammonia (9 mL) was stirred at room temperature for 4 h. All volatiles were removed *in vacuo* and the residue was co-evaporated with dry chloroform to afford pure compounds **14a–h**.

Diethyl [4-(carbamoyl)-1,2,3-triazol-1-yl]-methylphosphonate ***14a***

From **13a** (0.090 g, 0.325 mmol) the phosphonate **14a** (0.082 g, 96%) was obtained as a white powder. m.p.: 112–113°C; IR (KBr): $\nu = 3379, 3189, 2987, 2900, 1667, 1193, 1078, 1042\ cm^{-1}$; ^1H NMR (300 MHz, CD_3OD): $\delta = 7.84$ (s, 1H, HC5′); 4.07 (d, $J = 12.5$ Hz, 2H, PCH_2); 3.58–3.26 (m, 4H, $2 \times POCH_2CH_3$), 0.61 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 164.7$ (s, C=O); 143.5 (s, HC=C); 128.0 (s, HC=C); 62.3 (d, $J = 6.3$ Hz, POC); 48.5 (d, $J = 147.2$ Hz, PC); 17.2 (d, $J = 6.4$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 9.29$ ppm. Anal. calcd. for $C_8H_{15}N_4O_4P$: C, 36.65; H, 5.77; N, 21.37. Found: C, 36.44; H, 5.62; N, 21.12.

Diethyl 2-[4-(carbamoyl)-1,2,3-triazol-1-yl]-ethylphosphonate ***14b***

From **13b** (0.070 g, 0.240 mmol) the phosphonate **14b** (0.065 g, 99%) was obtained as a white powder. m.p.: 115–117°C; IR (KBr): $\nu = 3398, 2984, 2909, 2878, 1677, 1238, 1028\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.36$ (s, 1H, HC5′); 7.02 (brs, 1H, NH); 5.80 (brs, 1H, NH); 4.68 (dt, $J = 12.7$ Hz, $J = 7.4$ Hz, 2H, $PCCH_2$); 4.16–4.06 (m, 4H, $2 \times POCH_2CH_3$), 2.46 (dt, $J = 18.6$ Hz, $J = 7.4$ Hz, 2H, PCH_2); 1.31 (t, $J = 7.0$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 162.2$ (s, C=O); 142.9 (s, HC=C); 126.6 (s, HC=C); 62.4 (d, $J = 6.3$ Hz, POC); 45.2 (s, PC*C*); 27.3 (d, $J = 141.0$ Hz, PC); 16.6 (d, $J = 5.7$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.05$ ppm. Anal. calcd. for $C_9H_{17}N_4O_4P$: C, 39.13; H, 6.20; N, 20.28. Found: C, 39.29; H, 6.33; N, 20.23.

Diethyl 3-[4-(carbamoyl)-1,2,3-triazol-1-yl]-propylphosphonate ***14c***

From **13c** (0.090 g, 0.310 mmol) the phosphonate **14c** (0.083 g, 96%) was obtained as a white powder. m.p.: 110–112°C; IR (KBr): $\nu = 3417, 3186, 2980, 2907, 1648, 1238, 1038\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.25$ (s, 1H, HC5′); 7.24 (brs, 1H, NH); 6.52 (brs, 1H, NH); 4.54 (t, $J = 6.9$ Hz, 2H, $PCCCH_2$); 4.18–4.05 (m, 4H, $2 \times POCH_2CH_3$), 2.28 (dqu, $J = 15.3$ Hz, $J = 6.9$ Hz, 2H, $PCCH_2$); 1.76 (ddd, $J = 15.3$ Hz, $J = 8.0$ Hz, $J = 6.9$ Hz, 2H, PCH_2); 1.33 (t, $J = 7.1$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 164.6$ (s, C=O); 143.8 (s, HC=C); 127.8 (s, HC=C); 63.5 (d, $J = 6.6$ Hz, POC); 51.4 (d, $J = 17.4$ Hz, PCC*C*), 24.8 (d, $J = 4.6$ Hz, PC*C*); 23.2 (d, $J = 142.6$ Hz, PC); 16.9 (d, $J = 5.7$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 30.90$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_4P$: C, 41.38; H, 6.60; N, 19.30. Found: C, 41.50; H, 6.41; N, 19.33.

Diethyl 4-[4-(carbamoyl)-1,2,3-triazol-1-yl]-butylphosphonate ***14d***

From **13d** (0.068 g, 0.224 mmol) the phosphonate **14d** (0.064 g, 98%) was obtained as a white powder. m.p.: 87–89°C; IR (KBr): $\nu = 3418, 3180, 3039, 2983, 2934, 1656, 1242, 1031\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.16$ (s, 1H, HC5′); 7.17 (brs, 1H, NH); 6.20 (brs, 1H, NH); 4.44 (t, $J = 6.9$ Hz, 2H, $PCCCCH_2$); 4.18–4.02 (m, 4H, $2 \times POCH_2CH_3$), 2.19–2.05 (m, 2H, CH_2); 1.85–1.60 (m, 4H, $2 \times CH_2$); 1.34 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); 1.32 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 164.6$ (s, C=O); 143.8 (s, HC=C); 127.6 (s, HC=C); 63.4 (d, $J = 6.2$ Hz, POC); 51.0 (s, PCCC*C*); 31.7 (d, $J = 15.7$ Hz, PCC*C*), 25.3 (d, $J = 140.9$ Hz, PC); 20.4 (d, $J = 5.1$ Hz, PC*C*); 16.9 (d, $J = 6.1$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 31.90$ ppm. Anal. calcd. for $C_{11}H_{21}N_4O_4P$: C, 43.42; H, 6.96; N, 18.41. Found: C, 43.32; H, 7.09; N, 18.49.

Diethyl 1-hydroxy-2-[4-(carbamoyl)-1,2,3-triazol-1-yl]-ethylphosphonate ***14e***

From **13e** (0.060 g, 0.196 mmol) the phosphonate **14e** (0.054 g, 98%) was obtained as a white powder. m.p.: 95–97°C; IR (KBr): $\nu = 3416, 3206, 2984, 2931, 1636, 1217, 1048\ cm^{-1}$; ^1H NMR (300 MHz, CD_3OD): $\delta = 8.43$ (s, 1H, HC5′); 4.80 (ddd, $J = 14.4$ Hz, $J = 6.3$ Hz, $J = 3.3$ Hz, 1H, $PCCH_aH_b$); 4.62 (ddd, $J = 14.4$ Hz, $J = 9.6$ Hz, $J = 7.2$ Hz, 1H, $PCCH_aH_b$); 4.26–4.14 (m, 4H, $2 \times POCH_2CH_3$), 4.36 (dt, $J = 9.6$ Hz, $J = 3.3$ Hz, 1H, PC*H*(OH)); 1.35 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 164.7$ (s, C=O); 140.3 (s, HC=C); 129.0 (s, HC=C); 67.7 (d, $J = 167.7$ Hz, PC); 64.9 (d, $J = 7.4$ Hz, POC); 64.7 (d, $J = 7.4$ Hz, POC); 53.1 (d, $J = 10.0$ Hz, C-2); 17.0 (d, $J = 5.1$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 21.80$ ppm. Anal. calcd. for $C_9H_{17}N_4O_5P$: C, 36.99; H, 5.86; N, 19.17. Found: C, 37.12; H, 5.69; N, 19.20.

Diethyl 2-hydroxy-3-[4-(carbamoyl)-1,2,3-triazol-1-yl]-propylphosphonate ***14f***

From **13f** (0.076 g, 0.248 mmol) the phosphonate **14f** (0.061 g, 85%) was obtained as an amorphous solid. m.p.: 186–188°C; IR (KBr): $\nu = 3410, 3300, 2986, 2900, 1650, 1221, 1034\ cm^{-1}$; ^1H NMR (300 MHz, CD_3OD): $\delta = 8.37$ (s, 1H, HC5′); 4.66 (dd, $J = 13.8$ Hz, $J = 3.6$ Hz, 1H, $PCCCH_aH_b$); 4.44 (dd, $J = 13.8$ Hz, $J = 7.5$ Hz, 1H, $PCCCH_aH_b$); 4.20–4.06 (m, 4H, $2 \times POCH_2CH_3$), 2.22–1.97 (m, 2H, PCH_aH_b); 1.34 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); 1.33 (t, $J = 7.2$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 158.9$ (s, C=O); 140.9 (s, HC=C); 126.8 (s, HC=C); 67.6; 63.6 (d, $J = 6.8$ Hz, POC); 63.3 (d, $J = 6.8$ Hz, POC); 57.8 (d, $J = 14.2$ Hz, PCC*C*); 32.0 (d, $J = 141.4$ Hz, PC); 16.6 (d, $J = 6.5$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 29.68$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_5P$: C, 39.22; H, 6.25; N, 18.29. Found: C, 39.01; H, 6.13; N, 18.39.

Diethyl 2-{[4-(carbamoyl)-1,2,3-triazol-1-yl]ethoxy}-methylphosphonate ***14g***

From **13g** (0.100 g, 0.311 mmol) the phosphonate **14g** (0.095 g, 98%) was obtained as an amorphous solid. m.p.: 65–67°C; IR (KBr): $\nu = 3413, 3193, 2987, 2902, 1651, 1262, 1038\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.27$ (s, 1H, HC5′); 7.28 (brs, 1H, NH); 5.85 (brs, 1H, NH); 4.63 (t, $J = 4.8$ Hz, 2H, OCH_2CH_2N); 4.18–3.98 (m, 4H, $2 \times POCH_2CH_3$), 4.01 (t, $J = 4.8$ Hz, 2H, OCH_2CH_2N); 3.79 (d, $J = 8.1$ Hz, 2H, PCH_2O); 1.33 (t, $J = 7.0$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 162.2$ (s, C=O); 142.8 (s, HC=C); 127.0 (s, HC=C); 70.8 (d, $J = 10.3$ Hz, OCH_2CH_2N); 65.3 (d, $J = 166.1$ Hz, PC); 62.6 (d, $J = 6.5$ Hz, POC); 50.4 (s, OCH_2CH_2N); 16.5 (d, $J = 5.6$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.26$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_5P$: C, 39.22; H, 6.25; N, 18.29. Found: C, 39.39; H, 6.12; N, 18.14.

Diethyl 2-{[4-(carbamoyl)-1,2,3-triazol-1-yl]ethoxy}-ethylphosphonate ***14h***

From **13h** (0.092 g, 0.274 mmol) the phosphonate **14h** (0.085 g, 98%) was obtained as a colorless oil. IR (film): $\nu = 3403, 3176, 2983, 2930, 1660, 1231, 1032\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.32$ (s, 1H, HC5′); 7.19 (brs, 1H, NH); 5.96 (brs, 1H, NH); 4.60 (t, $J = 4.7$ Hz, 2H, OCH_2CH_2N); 4.14–4.04 (m, 4H, $2 \times POCH_2CH_3$), 3.84 (t, $J = 4.7$ Hz, 2H, OCH_2CH_2N); 3.79 (dt, $J = 13.1$ Hz, $J = 7.3$ Hz, 2H, PCH_2CH_2O); 2.08 (dt, $J = 18.6$ Hz, $J = 7.3$ Hz, 2H, PCH_2CH_2O); 1.31 (t, $J = 7.0$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 162.4$ (s, C=O); 142.7 (s, HC=C); 127.0 (s, HC=C); 68.7

(s, OCH_2CH_2N); 65.3 (d, $J = 1.7$ Hz, PCH_2CH_2O); 61.9 (d, $J = 6.6$ Hz, POC); 50.6 (s, OCH_2CH_2N); 26.9 (d, $J = 140.3$ Hz, PC); 16.5 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 28.99$ ppm. Anal. calcd. for $C_{11}H_{21}N_4O_5P$: C, 41.25; H, 6.61; N, 17.49. Found: C, 41.34; H, 6.49; N, 17.40.

*General procedure for synthesis of compounds **15a–h***

A mixture of diethyl [4-(methoxycarbonyl)-1,2,3-triazol-1-yl]alkylphosphonates **13a–h** (1.00 mmol) and 50% aqueous hydroxylamine (10 mmol) in ethanol (1 mL) was stirred at 30°C for 20 min. After evaporation of solvents the residue was purified by column chromatography on silica gel with chloroform–methanol (20:1 v/v) to give the corresponding hydroxamic acids **15a–h**.

*Diethyl [4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]-methylphosphonate **15a***

From **13a** (0.095 g, 0.343 mmol) the phosphonate **15a** (0.060 g, 63%) was obtained as an amorphous solid. m.p.: 147–149°C; IR (KBr): $\nu = 3265$, 3216, 2988, 2940, 1677, 1214, 1012 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.40$ (s, 1H, HC5′); 5.11 (d, $J = 13.3$ Hz, 2H, PCH_2); 4.23–4.13 (m, 4H, $2 \times POCH_2CH_3$), 1.32 (t, $J = 6.9$ Hz, 3H, $POCH_2CH_3$); 1.31 (t, $J = 6.9$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 160.0$ (s, C=O); 142.4 (s, HC=C); 128.0 (s, HC=C); 65.0 (d, $J = 6.4$ Hz, POC); 46.4 (d, $J = 154.6$ Hz, PC); 16.8 (d, $J = 6.9$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 17.97$ ppm. Anal. calcd. for $C_8H_{15}N_4O_5P$: C, 34.54; H, 5.43; N, 20.14. Found: C, 34.40; H, 5.19; N, 20.01.

*Diethyl 2-[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]-ethylphosphonate **15b***

From **13b** (0.100 g, 0.343 mmol) the phosphonate **15b** (0.060 g, 60%) was obtained as an amorphous solid. m.p.: 135–136°C; IR (KBr): $\nu = 3327$, 3110, 2977, 2929, 1657, 1120, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.08$ (brs, 1H, NH); 8.37 (s, 1H, HC5′); 4.69 (dt, $J = 11.9$ Hz, $J = 7.9$ Hz, 2H, $PCCH_2$); 4.18–4.06 (m, 4H, $2 \times POCH_2CH_3$), 2.47 (dt, $J = 18.6$ Hz, $J = 7.9$ Hz, 2H, PCH_2); 1.31 (t, $J = 7.0$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 160.4$ (s, C=O); 142.9 (s, HC=C); 127.7 (s, HC=C); 63.8 (d, $J = 6.6$ Hz, POC); 45.8 (d, $J = 3.1$ Hz, PCH_2CH_2); 27.3 (d, $J = 141.7$ Hz, PC); 16.8 (d, $J = 7.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 26.49$ ppm. Anal. calcd. for $C_9H_{17}N_4O_5P$: C, 36.99; H, 5.86; N, 19.17. Found: C, 36.72; H, 5.99; N, 19.33.

*Diethyl 3-[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]-propylphosphonate **15c***

From **13c** (0.107 g, 0.351 mmol) the phosphonate **15c** (0.100 g, 93%) was obtained as an amorphous solid. m.p.: 123–124°C; IR (KBr): $\nu = 3297$, 3230, 2980, 2928, 1657, 128, 1032 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.54$ (s, 1H, HC5′); 4.54 (t, $J = 7.5$ Hz, 2H, $PCCCH_2$); 4.16–4.02 (m, 4H, $2 \times POCH_2CH_3$), 2.29 (dqu, $J = 15.3$ Hz, $J = 7.5$ Hz, 2H, $PCCH_2$); 1.74 (ddd, $J = 15.3$ Hz, $J = 10.5$ Hz, $J = 7.5$ Hz, 2H, PCH_2); 1.32 (t, $J = 6.6$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 158.6$ (s, C=O); 140.8 (s, HC=C); 126.7 (s, HC=C); 62.3 (d, $J = 6.6$ Hz, POC); 50.6 (d, $J = 16.9$ Hz, PCC*C*), 23.6 (d, $J = 4.5$ Hz, PC*C*); 22.5 (d, $J = 142.6$ Hz, PC); 16.6 (d, $J = 5.7$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 31.57$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_5P$: C, 39.22; H, 6.25; N, 18.29. Found: C, 39.49; H, 6.48; N, 18.49.

*Diethyl 4-[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]-butylphosphonate **15d***

From **13d** (0.102 g, 0.319 mmol) the phosphonate **15d** (0.080 g, 78%) was obtained as an amorphous solid. m.p.: 116–117°C; IR (KBr): $\nu = 3310$, 3099, 2992, 2914, 1653, 1205, 10181 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.40$ (brs, 1H, NH); 8.43 (s, 1H, HC5′); 4.45 (t, $J = 7.1$ Hz, 2H, $PCCCCH_2$); 4.14–4.01 (m, 4H, $2 \times POCH_2CH_3$), 2.04 (qv, $J = 7.2$ Hz, 2H, $PCCCH_2$); 1.86–1.76 (m, 2H, PCH_2); 1.71–1.57 (m, 2H, $PCCH_2$); 1.28 (t, $J = 6.9$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 158.6$ (s, C=O); 140.8 (s, HC=C); 126.3 (s, HC=C); 62.0 (d, $J = 6.6$ Hz, POC); 50.2 (s, PCCC*C*); 30.7 (d, $J = 15.4$ Hz, PCC*C*), 24.8 (d, $J = 141.1$ Hz, P*C*); 19.6 (d, $J = 4.8$ Hz, PC*C*); 16.6 (d, $J = 6.0$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 32.61$ ppm. Anal. calcd. for $C_{11}H_{21}N_4O_5P$: C, 41.25; H, 6.61; N, 17.49. Found: C, 41.39; H, 6.89; N, 17.29.

*Diethyl 1-hydroxy-2-[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]ethylphosphonate **15e***

From **13e** (0.094 g, 0.307 mmol) the phosphonate **15e** (0.070 g, 74%) was obtained as amorphous solid. m.p.: 199–202°C; IR (KBr): $\nu = 3250$, 3166, 2981, 2927, 1659, 1209, 1044 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.40$ (s, 1H, HC5′); 4.80 (ddd, $J = 14.3$ Hz, $J = 6.5$ Hz, $J = 3.3$ Hz, 1H, $PCCH_aH_b$); 4.62 (ddd, $J = 14.3$ Hz, $J = 9.5$ Hz, $J = 6.9$ Hz, 1H, $PCCH_aH_b$); 4.35 (dt, $J = 9.5$ Hz, $J = 3.3$ Hz, 1H, P*C*H(OH)); 4.26–4.16 (m, 4H, $2 \times POCH_2CH_3$),1.35 (t, $J = 7.1$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (151 MHz, CD_3OD): $\delta = 159.2$ (s, C=O); 140.7 (s, HC=C); 127.0 (s, HC=C); 66.3 (d, $J = 166.1$ Hz, PC); 63.4 (d, $J = 6.9$ Hz, POC); 63.2 (d, $J = 6.9$ Hz, POC); 51.6 (d, $J = 10.3$ Hz, PC*C*); 15.4 (d, $J = 3.6$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 21.76$ ppm. Anal. calcd. for $C_9H_{17}N_4O_6P$: C, 35.07; H, 5.56; N, 18.18. Found: C, 34.89; H, 5.69; N, 18.10.

*Diethyl 2-hydroxy-3-[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]propylphosphonate **15f***

From **13f** (0.110 g, 0.342 mmol) the phosphonate **15f** (0.087 g, 79%) was obtained as an amorphous solid. m.p.: 143–145°C; IR (KBr): $\nu = 3408$, 3234, 3160, 2977, 2928, 1642, 1208, 1035 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): $\delta = 8.36$ (s, 1H, HC5′); 4.66 (dd, $J = 13.7$ Hz, $J = 3.1$ Hz, 1H, $PCCCH_aH_b$); 4.44 (d, $J = 13.7$ Hz, $J = 7.7$ Hz, 1H, $PCCCH_aH_b$); 4.38–4.30 (m, 1H, $PCCH_2$); 4.18–4.08 (m, 4H, $2 \times POCH_2CH_3$), 2.15 (ddd, $J = 18.6$ Hz, $J = 15.4$ Hz, $J = 5.4$ Hz, 1H, PCH_aH_b); 2.05 (ddd, $J = 18.4$ Hz, $J = 15.4$ Hz, $J = 7.2$ Hz, 1H, PCH_aH_b); 1.33 (dt, $J = 7.0$ Hz, $J = 0.5$ Hz, 3H, $POCH_2CH_3$); 1.33 (dt, $J = 7.0$ Hz, $J = 0.5$ Hz, 3H, $POCH_2CH_3$); ^{13}C NMR (75.5 MHz, CD_3OD): $\delta = 160.5$ (s, C=O); 141.9 (s, HC=C); 128.4 (s, HC=C); 66.6; 63.7 (d, $J = 6.5$ Hz, POC); 63.4 (d, $J = 6.5$ Hz, POC); 57.4 (d, $J = 14.6$ Hz, PCC*C*); 32.1 (d, $J = 140.6$ Hz, PC); 16.9 (d, $J = 6.3$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, CD_3OD): $\delta = 29.70$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_6P$: C, 37.27; H, 5.94; N, 17.39. Found: C, 37.43; H, 6.04; N, 17.26.

*Diethyl 2-{[4-(hydroxycarbamoyl)-1,2,3-triazol-1-yl]ethoxy}-methylphosphonate **15g***

From **13g** (0.100 g, 0.311 mmol) the phosphonate **15g** (0.071 g, 66%) was obtained as an yellowish oil. IR (film): $\nu = 3399$, 3214, 3153, 2987, 2910, 1662, 1221, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.02$ (brs, 1H, NH); 8.40 (s, 1H, HC5′); 4.63 (t, $J = 5.1$ Hz, 2H, OCH_2CH_2N); 4.18–4.09 (m, 4H, $2 \times POCH_2CH_3$), 4.00 (t, $J = 5.1$ Hz, 2H, OCH_2CH_2N); 3.81 (d, $J = 8.4$ Hz, 2H, PCH_2O); 1.30 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 162.6$ (s, C=O); 140.1 (s, HC=C); 129.2 (s, HC=C); 71.1 (d,

$J = 10.9$ Hz, OCH_2CH_2N); 65.2 (d, $J = 167.5$ Hz, PC); 63.2 (d, $J = 6.6$ Hz, POC); 50.6 (d, $J = 6.5$ Hz, OCH_2CH_2N); 16.6 (d, $J = 5.7$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 21.56$ ppm. Anal. calcd. for $C_{10}H_{19}N_4O_6P$: C, 37.27; H, 5.94; N, 17.39. Found: C, 37.39; H, 5.69; N, 17.42.

*Diethyl 2-{[4-(carbamoyl)-1,2,3-triazol-1-yl]ethoxy}-ethylphosphonate **15h***

From **13h** (0.102 g, 0.304 mmol) the phosphonate **15h** (0.082 g, 80%) was obtained as a colorless oil. IR (film): $\nu = 3417$, 3144, 2985, 2911, 1667, 1225, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 10.50$ (brs, 1H, NH); 8.45 (s, 1H, HC5′); 4.59 (t, $J = 4.5$ Hz, 2H, OCH_2CH_2N); 4.11–4.00 (m, 4H, $2 \times POCH_2CH_3$), 3.82 (t, $J = 4.5$ Hz, 2H, OCH_2CH_2N); 3.70 (dt, $J = 14.7$ Hz, $J = 7.0$ Hz, 2H, PCH_2CH_2O); 2.08 (dt, $J = 18.6$ Hz, $J = 7.0$ Hz, 2H, PCH_2CH_2O); 1.31 (t, $J = 7.2$ Hz, 6H, $2 \times POCH_2CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 158.7$ (s, C=O); 140.7 (s, HC=C); 127.0 (s, HC=C); 68.8 (s, OCH_2CH_2N); 65.3 (d, $J = 2.6$ Hz, PCH_2CH_2O); 62.3 (d, $J = 6.3$ Hz, POC); 50.6 (s, OCH_2CH_2N); 25.8 (d, $J = 140.9$ Hz, PC); 16.6 (d, $J = 6.3$ Hz, POC*C*); ^{31}P NMR (121.5 MHz, $CDCl_3$): $\delta = 29.65$ ppm. Anal. calcd. for $C_{11}H_{21}N_4O_6P$: C, 39.29; H, 6.29; N, 16.66. Found: C, 39.02; H, 6.15; N, 16.79.

Antiviral activity assays

The antiviral assays were based on inhibition of virus-induced cytopathicity in HEL [herpes simplex virus type 1 (HSV-1), HSV-2 (G), varicella-zoster virus (VZV), cytomegalovirus, vaccinia virus, and vesicular stomatitis virus], Vero (parainfluenza-3, reovirus-1, Sindbis, Coxsackie B4, and Punta Toro virus), HeLa (vesicular stomatitis virus, Coxsackie virus B4, and respiratory syncytial virus), MDCK (influenza A (H1N1 and H3N1) and influenza B virus), or CRFK (FHV; FIPV) cell cultures. Confluent cell cultures in microtiter 96-well plates were inoculated with 100 cell culture inhibitory dose-50 ($CCID_{50}$) of virus (one $CCID_{50}$ being the virus dose to infect 50% of the cell cultures) (or 20 plaque-forming units (PFU) for VZV) in the presence of varying concentrations (250, 50, 10 μM ...) of the test compounds. Viral cytopathicity was recorded as soon as it reached completion in the control virus-infected cell cultures that were not treated with the test compounds. The antiviral concentration was expressed as the EC_{50} or 50%-effective compound concentration required to inhibit virus-induced cytopathicity by 50%.

Cytotoxicity and cytostatic assay

The cytotoxicity of the test compounds was monitored as a microscopically visible alteration of cell morphology, and expressed as the MCC or compound concentration required to afford a microscopically detectable alteration of cell culture morphology.

The cytostatic activity of the test compounds was determined as the 50% cytostatic concentration (IC_{50}) or compound concentration required to inhibit cell proliferation by 50%. For this purpose, cells were seeded in 200-μL wells of 96-well microtiter plates and allowed to proliferate for 2 (L1210) or 3 (CEM, HeLa) days in the absence or presence of different serial concentrations of the test compounds. At the end of the exponential proliferation phase, the cells were counted by an automated Coulter ZI particle counter (Analis, Ghent, Belgium).

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