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*To the 80th Anniversary of B.I. Ionin*

# Synthesis of Adamantyl-Containing Cidofovir Analogs as Potential Antiviral Prodrugs with High Bioavailability Parameters

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**Abstract**—We report on preparation of potential nucleoside phosphonate prodrugs: 1-{3-hydroxy-2-[*O*-(adamantylalkyl)phosphorylmethoxy]propyl}cytosines containing two structural fragments providing antiviral activity, nucleoside phosphonate and adamantyl sites.

**Keywords:** acyclic nucleoside phosphonate, cidofovir, adamantane, synthesis

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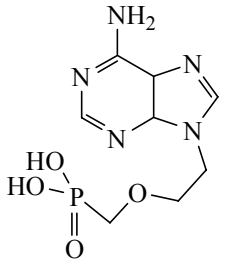
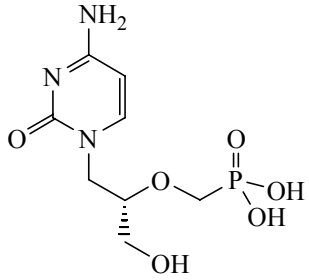
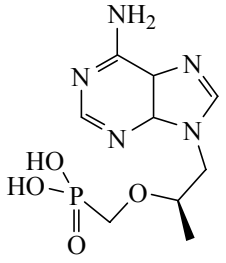
Nucleoside phosphonates (adefovir, cidofovir, tenofovir, and their analogs) are promising antiviral drugs of the new generation. These compounds has shown high efficacy against genomic DNA viruses [1–4] confirmed on a set of experimental models *in vitro* and *in vivo* [5–9].



Adefovir



Cidofovir



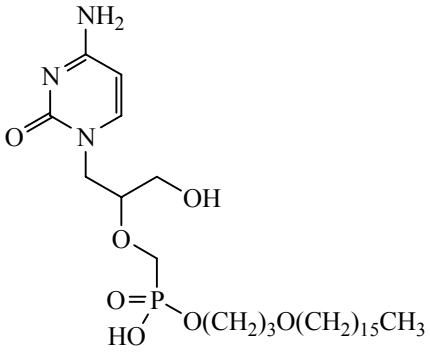
Tenofovir

Some nucleoside phosphonates also exhibit antiparasitic action, for example against *Plasmodium* [10]. The main drawback of these drugs is low bioavailability level [2], which makes their use possible exclusively by intravenous administration. This is due to the presence of the polar phosphoryl group in their molecules.

In this regard, one of the promising areas of medicinal chemistry development of prodrugs based on antiviral nucleoside phosphonates via modifications their phosphoryl group with the fragments that provide efficient targeted delivery of the compounds [11–13]. Such modifiers include short-chain peptides [14] as well as lipophilic radicals [15, 16] readily cleaved by the action of enzymatic systems of the organism, or hydrolyzed at cytoplasmic pH values.

One of successful examples of cidofovir modification has been preparation of the corresponding esters with higher alcohols and alkoxy alcohols; the products have revealed increased antiviral activity, enhanced oral bioavailability, and reduced toxicity [17, 18]. The most promising cidofovir derivative, hexadecyloxypropyl ester, known as brincidofovir, experimental drug originally developed primarily for treating

the cytomegalovirus and adenovirus infections, showed high activity against Ebola virus [19, 20].



Brincidofovir

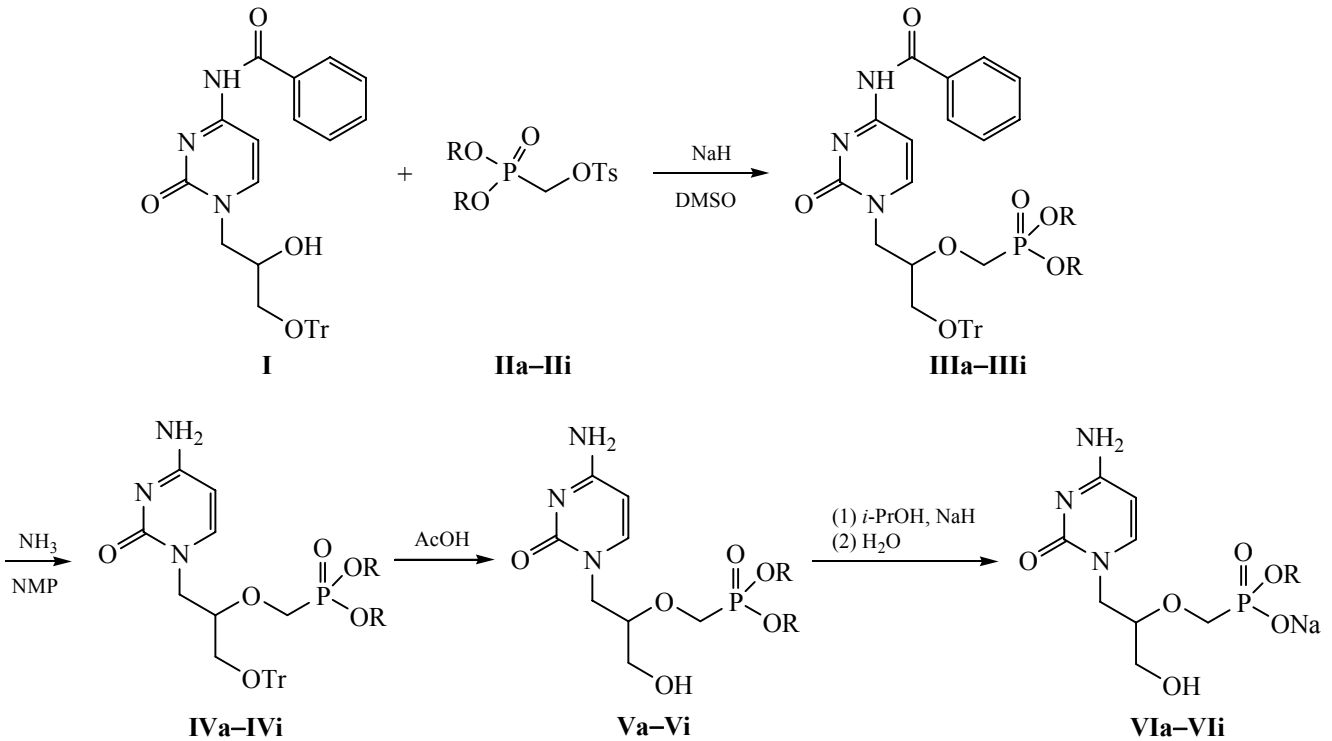
Using a modifier bearing antiviral activity as well opens the way to create the binary prodrugs: mechanism of their action and their targets differ from these of nucleoside phosphonates; hence, multiple steps of the virus replication cycle can be affected, and probability of resistant strains appearance will be reduced. We have proposed to use functional adamantane derivatives as such synergetic modifiers; these compounds affect on the (dis)assembly of virus particles. Viral proteins acting as ion channels and the cell membrane scaffold, can be the targets of the so constructed drugs [21–27].

We prepared cidofovir analogs **VIa**–**VIi** modified with lipophilic adamantyl-containing fragments via condensation of cytosine derivative **I** with tosyloxymethylphosphonates **IIa**–**IIi** followed by trityl and benzoyl deprotection.

Tosyloxymethylphosphonates **IIa**–**IIi** have been earlier prepared from the corresponding alcohols of adamantane series [28] (Scheme 1).

*O*-Alkylation of cytosine derivative **I** with tosyloxymethylphosphonates **IIa**–**IIi** proceeded in dimethylsulfoxide in the presence of sodium hydride to form 1-{3-trityloxy-2-[*O*,*O*-bis(adamantylalkyloxy)phosphorylmethoxy]propyl}-*N*-benzoylcitosines **IIIa**–**IIIi** with yields of 50–60%. Deprotection procedure consisted in sequential removal of the benzoyl and the trityl moieties; sequential deprotection was required to avoid migration of the benzoyl group to the third

**Scheme 1.**



R = 1-AdCH$_2$ (**a**), 1-AdCH$_2$CH$_2$ (**b**), 1-AdCH$_2$CH$_2$CH$_2$ (**c**), 1-AdOCH$_2$CH$_2$ (**d**), 1-AdOCH$_2$CH$_2$CH$_2$CH$_2$ (**e**), 3-CH$_3$CH$_2$-1-AdCH$_2$ (**f**), 3-CH$_3$CH$_2$-1-AdCH$_2$CH$_2$ (**g**), 3-CH$_3$CH$_2$-1-AdOCH$_2$CH$_2$CH$_2$CH$_2$ (**h**), 3-CH$_3$CH$_2$-1-AdOCH$_2$CH$_2$OCH$_2$CH$_2$ (**i**).

nitrogen atom of the nucleic base in acidic medium [29].

Benzoyl deprotection was carried out via alkaline hydrolysis with 20% aqueous ammonia in *N*-methylpyrrolidone. The reaction was performed in a sealed vial at 70°C during 4 h. The yield of compounds **IVa**–**IVi** at that stage was of 70–75%. Deprotection of **IVa**–**IVi** with 80% acetic acid at 60°C afforded 1-{3-hydroxy-2-[*O*,*O*-bis(adamantylalkyloxy)phosphorylmethoxy]propyl}citosines **Va**–**Vi**. Sodium salts of 1-{3-hydroxy-2-[(adamantylalkyloxy)phosphorylmethoxy]propyl}citosines **VIa**–**VIi** were prepared via sodium isopropoxide reaction with compounds **Va**–**Vi** followed by hydrolysis.

## EXPERIMENTAL

$^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded with a Bruker AM300 spectrometer [300.13 ($^1$H), 75.47 ($^{13}$C), and 121.49 MHz ($^{31}$P)]. Elemental analysis was performed with an EuroVector EA-3000 EA CHNS-analyzer.

Tosyloxymethylphosphonates **IIa**–**IIi** were synthesized as described elsewhere [28]; compound **I** was prepared following the procedure in [30].

**Synthesis of 1-{3-(trityloxy)-2-[(dialkoxyphosphoryl)methoxypropyl}-*N*-benzoylcitosines (IIIa–IIIi).** All the operations were carried out under argon. Cytosine derivative **I** (7.2 mmol) was added upon stirring to 60 mL of DMSO, and then 15 mL of DMSO was distilled off. Next, 0.84 g (21.0 mmol) of 60% suspension of sodium hydride in mineral oil was added in a single portion at room temperature. The reaction mixture was stirred at room temperature during 3 h. 9.5 mmol of tosylate **IIa**–**IIi** was then added and stirring was continued for 12 h at room temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated in vacuum. Yield 50–60%. The obtained compounds were used in the following syntheses without further purification.

**Synthesis of 1-{3-(trityloxy)-2-[(dialkoxyphosphoryl)methoxy]propyl}citosines (IVa–IVi).** A mixture of 35 mL of *N*-methylpyrrolidone, 5.2 mmol of compound **III**, and 10 mL of 20% aqueous ammonia solution was heated at 70°C in a sealed vial during 4 h. The reaction mixture was diluted with water and extracted with chloroform (3 × 50 mL). The organic layer was washed with water, dried over sodium sulfate, and evaporated in vacuum. Yield 70–75%. The obtained compounds were used in the following syntheses without further purification.

**1-{3-Hydroxy-2-[(dialkoxyphosphoryl)methoxy]propyl}citosines (Va–Vi).** A mixture of 6.7 mmol of compound **IV**, 40 mL of acetic acid, and 10 mL of water was heated at 60°C during 10 h. The reaction mixture was poured into 200 mL of icy water; sodium hydrocarbonate solution was added until neutralization, and the mixture was extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water, dried over sodium sulfate, and evaporated in vacuum. Compounds **Va**–**Vi** were isolated by column chromatography (silica gel, Kieselgel 60, methylene chloride–methanol, 0–10%, gradient elution).

**1-{3-Hydroxy-2-[di-(1-adamantylmethoxy)phosphorylmethoxy]propyl}citosine (Va).** Yield 61%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.55–2.05 m (30H, 2Ad), 3.55–3.65 m (6H, $3CH_2O$), 3.72–4.10 m (5H, $2CH_2$, CH), 5.76 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.42 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 27.99 (CH, Ad), 33.94 d (C, Ad, $^3J_{CP}$ 6.8 Hz), 36.94 ($CH_2$, Ad), 38.90 ($CH_2$, Ad), 49.69 ($CH_2N$), 59.80 ($CH_2OH$), 63.79 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 76.15 (Ad$\underline{CH_2}$O, $^2J_{CP}$ 7.5 Hz), 80.93 (CHO, $^3J_{CP}$ 9.0 Hz), 94.66 (CH=), 147.35 (CH=), 157.52 (C=O), 166.16 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.41 ppm. Found, %: C 62.50; H 7.86; N 7.39. $C_{30}H_{46}N_3O_6P$. Calculated, %: C 62.59; H 8.05; N 7.30.

**1-{3-Hydroxy-2-[di-(1-adamantylethoxy)phosphorylmethoxy]propyl}citosine (Vb).** Yield 67%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.55–2.05 m (34H, 2Ad, $2AdCH_2$), 3.55–4.21 m (12H, $4CH_2$, CH, OH, $NH_2$), 5.78 m (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.43 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 28.59 (CH, Ad), 31.87 (C, Ad) 37.01 ($CH_2$, Ad), 42.60 ($CH_2$, Ad), 44.48 d ($AdCH_2$, $^3J_{CP}$ 7.5 Hz), 49.70 ($CH_2N$), 59.80 ($CH_2OH$), 62.60 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 63.25 d ($CH_2O$, $^2J_{CP}$ 12.8 Hz), 81.03 d (CHO, $^3J_{CP}$ 9.0 Hz), 94.43 (CH=), 147.56 (CH=), 157.47 (C=O), 166.00 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.36 ppm. Found, %: C 63.59; H 8.29; N 7.09. $C_{32}H_{50}N_3O_6P$. Calculated, %: C 63.66; H 8.35; N 6.96.

**1-{3-Hydroxy-2-[di-(1-adamantylpropoxy)phosphorylmethoxy]propyl}citosine (Vc).** Yield 55%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.45–2.01 m (38H, 2Ad, $4CH_2$), 3.55–4.15 m (12H, $4CH_2$, CH, OH, $NH_2$),

5.75 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.44 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 24.08 d (AdCH$_2$<u>CH$_2$</u>CH$_2$O, $^3J_{CP}$ 5.3 Hz), 28.73 (CH, Ad), 32.00 (C, Ad), 37.21 ($CH_2$, Ad), 40.06 (Ad<u>CH$_2$</u>CH$_2$CH$_2$O), 42.47 ($CH_2$, Ad), 49.63 ($CH_2N$), 59.83 ($CH_2OH$), 64.21 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 67.78 (AdCH$_2$·CH$_2$<u>CH$_2$</u>O, $^2J_{CP}$ 6.8 Hz), 81.05 (CHO, $^3J_{CP}$ 9.0 Hz), 94.38 (CH=), 147.48 (CH=), 157.64 (C=O), 166.19 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.19 ppm. Found, %: C 64.57; H 8.52; N 6.72. $C_{34}H_{54}N_3O_6P$. Calculated, %: C 64.64; H 8.61; N 6.65.

**1-{3-Hydroxy-2-[di-(1-adamantyloxyethoxy)phosphorylmethoxy]propyl}citosine (Vd).** Yield 62%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.55– 2.20 m (30H, 2Ad), 3.55–4.22 m (18H, 7$CH_2$, CH, OH, $NH_2$), 5.75 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.50 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 30.54 (CH, Ad), 36.44 ($CH_2$, Ad), 41.57 ($CH_2$, Ad), 49.70 ($CH_2N$), 59.37 d (AdO<u>CH$_2$</u>CH$_2$O, $^3J_{CP}$ 5.3 Hz), 59.84 ($CH_2OH$), 64.29 d ($CH_2P$, $^1J_{CP}$ 167.0 Hz), 66.58 d (AdO·CH$_2$<u>CH$_2$</u>O, $^2J_{CP}$ 9.8 Hz), 72.87 (C, Ad), 80.97 (CHO, $^3J_{CP}$ 9.0 Hz), 94.12 (CH=), 147.90 (CH=), 157.50 (C=O), 166.01 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 23.17 ppm. Found, %: C 60.39; H 7.82; N 6.69. $C_{32}H_{50}N_3O_8P$. Calculated, %: C 60.46; H 7.93; N 6.61.

**1-{3-Hydroxy-2-[di-(1-adamantyloxybuthoxy)phosphorylmethoxy]propyl}citosine (Ve).** Yield 60%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.52–2.18 m (38H, 2Ad, 4$CH_2$), 3.38–4.15 m (18H, 7$CH_2$, CH, OH, $NH_2$), 5.77 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.43 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 26.64 ($CH_2$), 27.73 d ($CH_2$, $^3J_{CP}$ 6.8 Hz), 30.55 (CH, Ad) 36.54 ($CH_2$, Ad), 41.68 ($CH_2$, Ad), 49.84 ($CH_2N$), 59.06 (AdO<u>CH$_2$</u>), 59.95 (<u>CH$_2$</u>OH), 64.08 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 66.61 ($CH_2O$, $^2J_{CP}$ 6.8 Hz), 72.09 (C, Ad), 80.96 d (CHO, $^3J_{CP}$ 10.5 Hz), 94.24 (CH=), 147.55 (CH=), 157.53 (C=O), 166.21 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.55 ppm. Found, %: C 62.42; H 8.37; N 6.14. $C_{36}H_{58}N_3O_8P$. Calculated, %: C 62.50; H 8.45; N 6.07.

**1-{3-Hydroxy-2-[di-(3-ethyl-1-adamantylmethoxy)-phosphorylmethoxy]propyl}citosine (Vf).** Yield 57%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.76 t (6H, 2$CH_3$, $^3J_{HH}$ 7.0 Hz), 1.08–1.62 m (28H, $CH_2$, Ad), 2.08 s (4H, 4CH, Ad), 3.55–3.65 m (6H, 3$CH_2O$), 3.72–4.12 m (8H, 2$CH_2$, CH, OH, $NH_2$), 5.78 d (1H, CH= $^3J_{HH}$ 7.5 Hz), 7.43 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 7.05 ($CH_3$), 28.47 (CH, Ad), 32.62 (C, Ad), 34.77 d (C, Ad, $^3J_{CP}$ 6.0 Hz), 36.28 ($CH_2$, Et), 36.56 ($CH_2$, Ad), 38.64 ($CH_2$, Ad), 41.32 ($CH_2$, Ad), 43.31 ($CH_2$, Ad), 49.66 ($CH_2N$), 59.78 ($CH_2OH$), 63.85 d ($CH_2P$, $^1J_{CP}$ 167.0 Hz), 76.05 d ($CH_2O$, $^2J_{CP}$ 7.5 Hz), 80.96 d (CHO, $^3J_{CP}$ 10.0 Hz), 94.56 (CH=), 147.43 (CH=), 157.56 (C=O), 166.10 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.38 ppm. Found, %: C 64.61; H 8.57; N 6.72. $C_{34}H_{54}N_3O_6P$. Calculated, %: C 64.64; H 8.61; N 6.65.

**1-{3-Hydroxy-2-[di-(3-ethyl-1-adamantylethoxy)-phosphorylmethoxy]propyl}citosine (Vg).** Yield 62%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.77 t (6H, 2$CH_3$, $^3J_{HH}$ 7.0 Hz), 1.08–1.62 m (32H), 2.08 s (4H, 4CH, Ad), 3.55–4.20 m (14H, 5$CH_2$, CH, OH, $NH_2$), 5.70 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.47 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 7.05 ($CH_3$), 29.03 (CH, Ad), 32.59 (C, Ad), 32.98 (C, Ad), 36.40 ($CH_2$, Et), 36.62 ($CH_2$, Ad), 41.32 ($CH_2$, Ad), 42.27 ($CH_2$, Ad), 44.30 d ($CH_2$, $^3J_{CP}$ 4.5 Hz), 47.24 ($CH_2$, Ad), 49.62 ($CH_2N$), 59.78 ($CH_2OH$), 62.60 d ($CH_2P$, $^1J_{CP}$ 166.0 Hz), 63.25 d ($CH_2O$, $^2J_{CP}$ 12.7 Hz), 81.07 (CHO, $^3J_{CP}$ 9.0 Hz), 94.01 (CH=), 147.78 (CH=), 157.61 (C=O), 166.02 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.41 ppm. Found, %: C 65.44; H 8.82; N 6.43. $C_{36}H_{58}N_3O_6P$. Calculated, %: C 65.53; H 8.86; N 6.37.

**1-{3-Hydroxy-2-[di-(3-ethyl-1-adamantyloxy-buthoxy)phosphorylmethoxy]propyl}citosine (Vh).** Yield 55%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.71 t (6H, 2$CH_3$, $^3J_{HH}$ 7.0 Hz), 1.18 q (4H, 2$CH_2$, $^3J_{HH}$ 7.0 Hz), 1.30–1.70 m (56H, Ad, 4$CH_2$), 2.18 s (4H, 4CH, Ad), 3.38–4.18 m (18H, 7$CH_2$, CH, OH, $NH_2$), 5.74 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 7.45 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 7.21 ($CH_3$), 26.68 ($CH_2$), 27.73 d ($CH_2$, $^3J_{CP}$ 5.3 Hz), 30.60 (CH, Ad), 35.82 ($CH_2$, Et), 35.95 (C, Ad), 36.18 ($CH_2$, Ad), 40.99 d ($CH_2$, Ad), 41.21 ($CH_2$, Ad), 46.04 ($CH_2$, Ad), 49.81 ($CH_2N$), 59.21 ($CH_2OH$), 59.91 ($CH_2O$), 64.10 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 66.63 d ($CH_2O$, $^2J_{CP}$ 8.3 Hz), 73.06 (C, Ad), 80.97 (CHO, $^3J_{CP}$ 9.0 Hz), 94.18 (CH=), 147.60 (CH=), 157.54 (C=O), 166.18 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 22.26 ppm. Found, %: C 64.19; H 8.82; N 5.54. $C_{40}H_{66}N_3O_8P$. Calculated, %: C 64.23; H 8.89; N 5.62.

**1-{3-Hydroxy-2-[di-(3-ethyl-1-adamantyloxy-ethylethoxy)phosphorylmethoxy]propyl}citosine (Vi).** Yield 57%. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.72 t (6H, 2$CH_3$, $^3J_{HH}$ 7.0 Hz), 1.16 q (4H, 2$CH_2$, $^3J_{HH}$ 7.0 Hz), 1.30–1.65 m (24H, Ad), 2.20 s (4H, Ad), 3.55–4.30 m (26H, 11$CH_2$, CH, OH, $NH_2$), 5.81 d (1H,

CH=, $^3J_{HH}$ 7.5 Hz), 7.48 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 7.20 ($CH_3$), 30.59 (CH, Ad), 35.87 ($CH_2$, Et) 35.92 (C, Ad), 36.10 ($CH_2$, Ad), 40.92 ($CH_2$, Ad), 41.09 ($CH_2$, Ad), 45.89 ($CH_2$, Ad), 49.83 ($CH_2N$), 59.53 ($CH_2O$), 59.93 ($CH_2OH$), 64.01 d ($CH_2P$, $^1J_{CP}$ 168.0 Hz), 65.60 d ($CH_2O$, $^2J_{CP}$ 6.8 Hz), 70.29 d ($CH_2O$, $^3J_{CP}$ 6.0 Hz), 70.33 ($CH_2O$), 71.41 ($CH_2O$), 73.61 (C, Ad), 80.77 d (CHO, $^3J_{CP}$ 9.0 Hz), 94.26 (CH=), 147.80 (CH=), 157.39 (C=O), 166.13 ($CNH_2$). $^{31}$P NMR spectrum ($CDCl_3$): $\delta_P$ 23.24 ppm. Found, %: C 61.52; H 8.47; N 5.48. $C_{40}H_{66}N_3O_{10}P$. Calculated, %: C 61.60; H 8.53; N 5.39.

**Sodium salts of 1-{3-hydroxy-2-[(alkoxyphosphoryl)methoxy]propyl}citosines (VIa–VIi).** A suspension of 6.0 mmol of sodium hydride in mineral oil was added to a mixture of 50 mL of propan-2-ol and 0.5 mL of water. After hydrogen evolution ceased, a solution of 6.6 mmol of compound **V** in 50 mL of propan-2-ol was added. The reaction mixture was refluxed during 0.5 h. After cooling, the reaction product was filtered off and dried.

**Sodium salt of 1-{3-hydroxy-2-[(1-adamantylmethoxyphosphoryl)methoxy]propyl}citosine (VIa).** Yield 51%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.45–1.87 m (15H, Ad), 3.32–3.85 m (9H, 4$CH_2$, CH), 5.65 d (1H, =CH, $^3J_{HH}$ 7.5 Hz), 6.15 br.s (1H, OH), 7.10 br.s (2H, $NH_2$), 7.52 d (1H, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 27.64 (CH, Ad), 33.41 d (C, Ad, $^3J_{CP}$ 6.8 Hz), 36.78 ($CH_2$, Ad), 38.89 ($CH_2$, Ad), 49.63 ($CH_2N$), 60.30 ($CH_2OH$), 66.20 d ($CH_2P$, $^1J_{CP}$ 153.0 Hz), 73.93 d ($CH_2O$, $^2J_{CP}$ 6.0 Hz), 80.36 d (CHO, $^3J_{CP}$ 6.0 Hz), 92.99 (CH=), 146.94 (CH=), 156.38 (C=O), 165.98 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.41 ppm. Found, %: C 50.71; H 6.42; N 9.46. $C_{19}H_{29}N_3NaO_6P$. Calculated, %: C 50.78; H 6.50; N 9.35.

**Sodium salt of 1-{3-hydroxy-2-[(1-adamantylethoxyphosphoryl)methoxy]propyl}citosine (VIb).** Yield 67%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.35–1.95 m (17H, Ad, $CH_2$), 3.21–4.32 m (9H, 4$CH_2$, CH), 5.64 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6,19 br.s (1H, OH), 7.12 br.s (2H, $NH_2$), 7.51 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 28.01 (CH, Ad), 31.27 (C, Ad), 36.62 ($CH_2$, Ad), 42.10 ($CH_2$, Ad), 44.84 d (Ad$\underline{CH_2}$, $^3J_{CP}$ 6.0 Hz), 49.54 ($CH_2N$), 59.26 d ($CH_2O$, $^2J_{CP}$ 5.3 Hz), 60.50 ($\underline{CH_2}OH$), 65.53 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 80.53 d (CHO, $^3J_{CP}$ 6.0 Hz), 92.97 (CH=), 146.91 (CH=), 156.32 (C=O), 165.96 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.38 ppm. Found, %: C 51.79; H 6.72; N 9.17. $C_{20}H_{31}N_3NaO_6P$. Calculated, %: C 51.83; H 6.74; N 9.07.

**Sodium salt of 1-{3-hydroxy-2-[(1-adamantylpropoxyphosphoryl)methoxy]propyl}citosine (VIc).** Yield 55%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.05–1.91 m (19H, Ad, 2$CH_2$), 3.25–3.38 m (9H, 4$CH_2$, CH), 5.63 d (1H, CH, $^3J_{HH}$ 7.5 Hz), 6.31 br.s (1H, OH), 7.12 br.s (2H, $NH_2$), 7.52 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 24.02 d ($CH_2$, $^3J_{CP}$ 5.3 Hz), 28.04 (CH, Ad), 31.48 (C, Ad), 36.68 ($CH_2$, Ad), 41.91 ($CH_2$, Ad), 49.71 ($CH_2N$), 60.51 ($CH_2OH$), 64.29 d ($CH_2O$, $^2J_{CP}$ 6.8 Hz), 67.78 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 80.44 d (CHO, $^3J_{CP}$ 5.3 Hz), 92.86 (CH=), 146.95 (CH=), 156.25 (C=O), 165.96 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.11 ppm. Found, %: C 52.72; H 6.91; N 8.91. $C_{21}H_{33}N_3NaO_6P$. Calculated, %: C 52.83; H 6.97; N 8.80.

**Sodium salt of 1-{3-hydroxy-2-[(1-adamantyloxyethoxyphosphoryl)methoxy]propyl}citosine (VId).** Yield 65%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.55–2.20 m (15H, Ad), 3.25–3.71 m (11H, 5$CH_2$, CH), 5.65 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.21 br.s (1H, OH), 7.12 br.s (2H, $NH_2$), 7.55 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 29.83 (CH, Ad), 35.93 ($CH_2$, Ad), 41.09 ($CH_2$, Ad), 49.60 ($CH_2N$), 59.83 d ($CH_2O$, $^3J_{CP}$ 6.0 Hz), 60.62 ($CH_2OH$), 63.53 d ($CH_2O$, $^2J_{CP}$ 6.0 Hz), 66.73 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 71.22 (C, Ad), 80.55 d (CHO, $^3J_{CP}$ 6.0 Hz), 92.89 (CH=), 146.97 (CH=), 156.26 (C=O), 165.96 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.39 ppm. Found, %: C 50.02; H 6.41; N 8.81. $C_{20}H_{31}N_3NaO_7P$. Calculated, %: C 50.10; H 6.52; N 8.76.

**Sodium salt of 1-{3-hydroxy-2-[(1-adamantyloxybuthoxyphosphoryl)methoxy]propyl}citosine (VIe).** Yield 60%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.35–2.15 m (19H, Ad, 2$CH_2$), 3.21–3.81 m (11H), 5.64 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.07 s (1H, OH), 6.91–7.22 m (2H, $NH_2$), 7.54 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 26.70 ($CH_2$), 27.72 d ($CH_2$, $^3J_{CP}$ 6.0 Hz), 29.39 (CH, Ad), 35.98 ($CH_2$, Ad), 41.18 ($CH_2$, Ad), 49.54 ($CH_2N$), 58.73 ($CH_2O$), 60.44 ($CH_2OH$), 63.26 d ($CH_2O$, $^2J_{CP}$ 6.0 Hz), 66.52 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 70.88 (C, Ad), 80.50 d (CHO, $^3J_{CP}$ 6.8 Hz), 93.05 (CH=), 146.88 (CH=), 156.37 (C=O), 165.98 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): 14.29 ppm. Found, %: C 51.96; H 6.90; N 8.34. $C_{22}H_{35}N_3NaO_7P$. Calculated, %: C 52.07; H 6.95; N 8.28.

**Sodium salt of 1-{3-hydroxy-2-[(3-ethyl-1-adamantylmethoxyphosphoryl)methoxy]propyl}citosine (VIf).** Yield 57%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.76 t (3H, $CH_3$, $^3J_{HH}$ 7.0 Hz), 1.07–1.61 m (14H, 12H, Ad, $CH_2$), 2.01 s (2H, Ad), 3.18–3.82 m (9H, 4$CH_2$, CH), 5.62 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.32 s (1H, OH), 6.90–7.22 m (2H, $NH_2$), 7.51 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 6.93 ($CH_3$), 28.08 (CH, Ad), 32.12 (C, Ad), 34.18 d (C, Ad, $^3J_{CP}$ 6.0 Hz), 35.93 ($CH_2$, Ad), 36.42 ($CH_2$, Ad), 38.63 ($CH_2$), 41.12 ($CH_2$, Ad), 43.32 ($CH_2$, Ad), 49.73 ($CH_2N$), 60.55 ($CH_2OH$), 66.39 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 73.74 d ($CH_2O$, $^3J_{CP}$ 6.0 Hz), 80.42 d (CHO, $^3J_{CP}$ 5.3 Hz), 92.77 (CH=), 146.98 (CH=), 156.21 (C=O), 165.94 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.32 ppm. Found, %: C 52.74; H 6.91; N 8.87. $C_{21}H_{33}N_3NaO_6P$. Calculated, %: C 52.83; H 6.97; N 8.80.

**Sodium salt of 1-{3-hydroxy-2-[(3-ethyl-1-adamantylethoxyphosphoryl)methoxy]propyl}citosine (VIg).** Yield 62%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.76 t (3H, $CH_3$, $^3J_{HH}$ 7.0 Hz), 1.03–1.61 m (20H, 12H, Ad, 2$CH_2$), 1.93 s (2H, Ad), 3.15–3.85 m (9H, 4$CH_2$, CH), 5.63 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.33 s (1H, OH), 6.80–7.15 m (2H, $NH_2$), 7.53 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 6.87 ($CH_3$), 28.42 (CH, Ad), 31.95 (C, Ad), 32.39 (C, Ad), 35.84 ($CH_2$, Et) 36.22 ($CH_2$, Ad), 40.93 ($CH_2$, Ad), 41.74 ($CH_2$, Ad) 46.78 ($CH_2$), 49.67 ($CH_2N$), 59.20 d ($CH_2O$, $^2J_{CP}$ 5.3 Hz), 60.76 ($CH_2OH$), 66.71 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 80.62 d (CHO, $^3J_{CP}$ 4.5 Hz), 92.78 (CH=), 146.95 (CH=), 156.18 (C=O), 165.95 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.24 ppm. Found, %: C 53.70; H 7.09; N 8.64. $C_{22}H_{35}N_3NaO_6P$. Calculated, %: C 53.76; H 7.18; N 8.55.

**Sodium salt of 1-{3-hydroxy-2-[(3-ethyl-1-adamantyloxybuthoxyphosphoryl)methoxy]propyl}citosine (VIh).** Yield 55%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.75 t (3H, $CH_3$, $^3J_{HH}$ 7.0 Hz), 1.12 q (2H, $CH_2$, $^3J_{HH}$ 7.0 Hz), 1.31–1.69 m (28H, Ad, 2$CH_2$), 2.11 s (2H, Ad), 3.21–3.81 m (11H, 5$CH_2$, CH), 5.67 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.17 s (1H, OH), 6.90–7.20 m (2H, $NH_2$), 7.52 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 7.02 ($CH_3$), 26.71 ($CH_2$), 27.74 d ($CH_2$, $^3J_{CP}$ 6.0 Hz), 29.88 (CH, Ad), 35.15 (C, Ad), 35.38 ($CH_2$, Et), 35.60 ($CH_2$, Ad), 40.42 ($CH_2$, Ad), 40.73 ($CH_2$, Ad), 45.54 ($CH_2$, Ad), 49.58 ($CH_2N$), 58.87 ($CH_2O$), 60.51 ($CH_2OH$), 63.22 d ($CH_2O$, $^2J_{CP}$ 6.0 Hz), 66.57 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 71.83 (C, Ad), 80.51 (CHO, $^3J_{CP}$ 6.8 Hz), 92.98 (CH=), 146.93 (CH=), 156.31 (C=O), 165.98 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.27 ppm. Found, %: C 53.79; H 7.31; N 7.92. $C_{24}H_{39}N_3NaO_7P$. Calculated, %: C 53.83; H 7.34; N 7.85.

**Sodium salt of 1-{3-hydroxy-2-[(3-ethyl-1-adamantyloxyethylethoxyphosphoryl)methoxy]propyl}citosine (VIi).** Yield 57%. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 0.77 t (3H, $CH_3$, $^3J_{HH}$ 7.0 Hz), 1.19 q (2H, $CH_2$, $^3J_{HH}$ 7.0 Hz), 1.31–1.67 m (12H, Ad), 2.15 s (2H, Ad), 3.18–3.82 m (15H, 7$CH_2$, CH), 5.61 d (1H, CH=, $^3J_{HH}$ 7.5 Hz), 6.14 s (1H, OH), 6.85–7.19 m (2H, $NH_2$), 7.51 d (1H, CH=, $^3J_{HH}$ 7.5 Hz). $^{13}$C NMR spectrum (DMSO-$d_6$), $\delta_C$, ppm: 6.99 ($CH_3$), 29.87 (CH, Ad), 35.17 (C, Ad), 35.33 ($CH_2$, Et), 35.52 ($CH_2$, Ad), 40.34 ($CH_2$, Ad), 40.56 ($CH_2$, Ad), 45.35 ($CH_2$, Ad), 49.55 ($CH_2N$), 58.92 ($CH_2O$), 60.51 ($CH_2OH$), 62.68 d ($CH_2O$, $^3J_{CP}$ 6.0 Hz), 65.60 ($CH_2O$), 67.26 d ($CH_2P$, $^1J_{CP}$ 151.0 Hz), 70.80 d ($CH_2O$, $^2J_{CP}$ 6.0 Hz), 72.32 (C, Ad), 80.44 d (CHO, $^3J_{CP}$ 6.0 Hz), 92.95 (CH=), 146.96 (CH=), 156.27 (C=O), 165.96 ($CNH_2$). $^{31}$P NMR spectrum (DMSO-$d_6$): $\delta_P$ 14.40 ppm. Found, %: C 52.15; H 7.03; N 7.71. $C_{24}H_{39}N_3NaO_8P$. Calculated, %: C 52.26; H 7.13; N 7.62.

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