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SYNTHESIS AND ANTIVIRAL PROPERTIES OF AZA-ANALOGUES OF *ACYCLOVIR*

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□ *Aza-analogues of* Acyclovir *were obtained from* N-*(2-pivaloyloxyethyl)*-N-*(pivaloyloxymethyl)*-p-*toluenesulfonamide via a one-pot base silylation/nucleoside coupling procedure. The antiviral activities of all aza-nucleosides in vitro against a variety of viruses were evaluated. None of these compounds displayed any specific antiviral effects.*

Keywords Antiviral agents; Acyclic nucleosides; Aza-nucleosides; *Acyclovir* analogues

INTRODUCTION

Some acyclic nucleosides play a very important role in antiviral[1] and antitumor[2] therapy; for example, *Acyclovir*, *Ganciclovir*, and their prodrugs (e.g., *Valacyclovir* and *Valganciclovir*, respectively) are used for the clinical treatment of herpes virus infections.[1,3] Consequently, various modifications have been made to the parent structures,[4,5] but there is a lack of information on replacement of the oxygen atom by nitrogen. Generally there is not much work on the synthesis and biological (i.e., antitumor,[6b,e,f] antibacterial[6g] or antiviral[6o,p]) activities of acyclic nucleosides possessing a nitrogen atom at the 2′-position, named acyclic aza-nucleosides. The majority of them are aminoacid or peptide derivatives of pyrimidine nucleobases, mostly 5-fluorouracil.[6]

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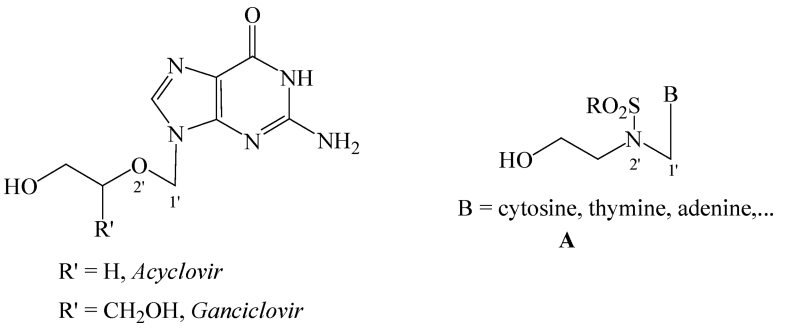


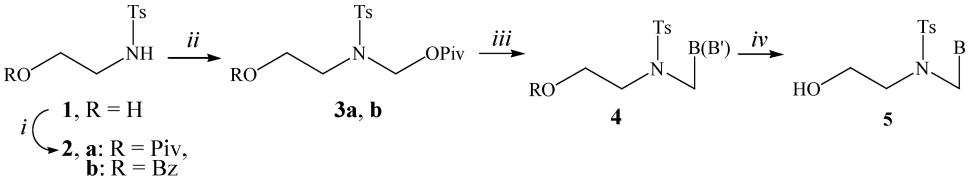
FIGURE 1 The general structure of aza-analogues of *Acyclovir* (**A**).

Recently, we have shown that acyclic aza-nucleosides may be obtained easily from *N*-(pivaloyloxymethyl)sulfonamides through a one-pot base silylation/nucleoside coupling procedure.[7] Using this methodology, we successfully have accomplished the synthesis of aza–analogues of *Ganciclovir*. Here, we describe the utility of this approach for the synthesis of aza-analogues of *Acyclovir* (**A**) as well as the results of their antiviral screening (Figure 1).

RESULTS AND DISCUSSION

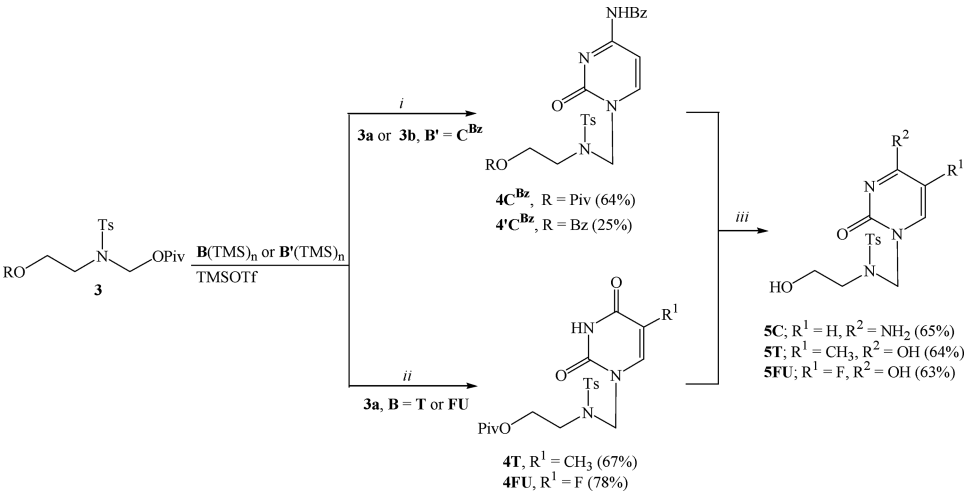
Synthesis

As the first target we set up the synthesis of series of the aza–analogues of *Acyclovir* possessing *p*-toluenesulfonyl substituent at the 2′-nitrogen atom (Scheme 1, compounds of type **5**). Thus, *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide[8] **1**, readily available from 2-aminoethanol, was converted into the key *N*-(pivaloyloxymethyl)sulfonamides **3a** and **3b** in two steps through *O*-benzoylation or *O*-pivaloylation followed by the alkylation with chloromethyl pivalate in the presence of potassium carbonate in dry DMF at room temperature. The compounds **3a** and **3b** were obtained in 77% and 73% overall yield, respectively; crude **3** were pure enough to be used for the synthesis of aza-nucleosides **4**.



Piv = C(O)Bu^t, Ts = tosyl, B = unprotected nucleobase, B' = protected nucleobase

SCHEME 1 Reagents and conditions: (*i*) BzCl or PivCl, Py, rt, 1 day (**2a**, 90%; **2b**, 91%); (*ii*) $PivOCH_2Cl$, K_2CO_3, DMF, rt, 5 days (**3a**, 85%; **3b**, 80%); (*iii*) $B(TMS)_n$ or $\mathbf{B}'(TMS)_n$, Lewis acid; (*iv*) NH_3 aq/MeOH.



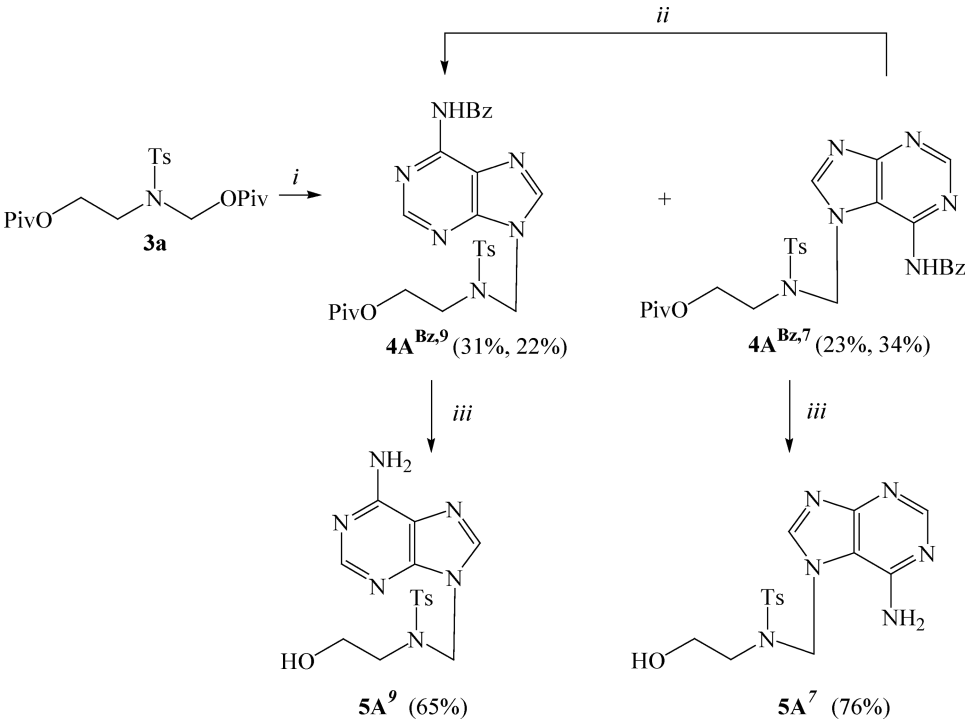
SCHEME 2 Reagents and conditions: (*i*) a) $\mathbf{C}^{Bz}$, BSA, MeCN, rt, 1 hour; b) **3a** or **3b**, TMSOTf, MeCN, rt, 3 days; (*ii*) a) **T** or **FU**, BSA, MeCN, rt, 1 h; b) **3a**, TMSOTf, MeCN, rt, 3 days; (*iii*) NH_3 aq/MeOH, 70°C, 5 days.

A one-pot base silylation/nucleoside coupling procedure was employed for the synthesis of aza-analogues of *Acyclovir* **4**, but the reaction conditions varied somewhat depending on the sort of base employed (for details see Schemes 2–4).[9] First the coupling of **3a** and **3b** with N^4-benzoylcytosine ($\mathbf{C}^{Bz}$) was examined (Scheme 2, path *i*). Thus, $\mathbf{C}^{Bz}$ was treated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in dry acetonitrile at room temperature for 1 hour, then the corresponding **3** and trimethylsilyl triflate (TMSOTf) were added consecutively and the resulted mixture was kept at room temperature for 3 days. The nucleoside $\mathbf{4C}^{Bz}$ (R = Piv) was obtained in much higher yield (64%) and it was more easily purified than $\mathbf{4'C}^{Bz}$ (R = Bz, 25%); so for the next nucleoside couplings only *O*-pivaloyl sulfonamide **3a** was utilized.

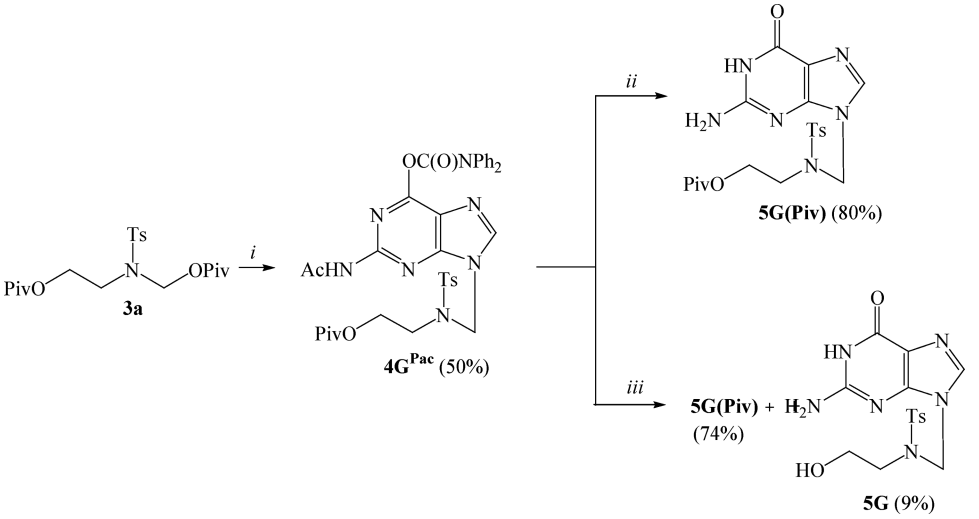
Under similar conditions **3a** was condensed with thymine (**T**) or 5-fluorouracil (**FU**) to give the corresponding aza-nucleosides **4T** or **4FU** in 67% or 78% yield, respectively (Scheme 2, path *ii*). Heating of $\mathbf{4C}^{Bz}$, **4T**, or **4FU** with ammonium hydroxide in methanol at 70°C (sealed tube) for 5 days afforded the deprotected nucleosides **5C**, **5T**, or **5FU**, respectively; the yields exceeded 60%.

The coupling of **3a** with N^6–benzoyladenine ($\mathbf{A}^{Bz}$) was conducted in the presence of tin(IV) chloride (Scheme 3).[9] The mixture of regioisomeric adenine N^9-($\mathbf{4A}^{Bz,9}$) and N^7-derivative ($\mathbf{4A}^{Bz,7}$) was obtained in approximately 55% summary yield and variable N^9/N^7 ratio; this reaction was repeated twice to yield, under the same conditions, the $\mathbf{4A}^{Bz,9}/\mathbf{4A}^{Bz,7}$ mixtures in a 1.3/1 and 1/1.5 ratio, respectively.

To convert $\mathbf{4A}^{Bz,7}$ into $\mathbf{4A}^{Bz,9}$, the N^7-isomer was heated in toluene at 80°C in the presence of TMSOTf until the reaction was completed.[10]



SCHEME 3 Reagents and conditions: *i*) a) $\mathbf{A}^{\mathbf{Bz}}$, BSA, MeCN, rt, 1 hour; b) **3a**, $SnCl_4$, MeCN, rt, 3 days; (*ii*) TMSOTf, toluene, 80°C, 2 hours (16%); (*iii*) NH_3 aq/MeOH, 70°C, 3 days.



SCHEME 4 Reagents and conditions: (*i*) a) $\mathbf{G}^{\mathbf{Pac}}$, BSA, CH_2Cl_2, 80°C, 15 minutes; b) **3a**, TMSOTf, toluene, 80°C, 1 hour; (*ii*) NH_3 aq/MeOH, rt, 1 day; (*iii*) NH_3 aq/MeOH, 70°C, 7 days.

Under these conditions most of the substrate decomposed and **4A^{Bz,9}** was obtained in low yield (16%). The deprotected derivative **5A^{9}** or **5A^{7}** was obtained by heating **4A^{Bz,9}** or **4A^{Bz,7}** in methanol with ammonium hydroxide at 70°C for 3 days.

Since our previous attempts to obtain the guanine derived aza-nucleosides using the procedure described above were unsuccessful,[7] we employed the original Robins' procedure[11] for the synthesis of the corresponding guanine derivative **4G^{Pac}** (Scheme 4). Thus, N^2-acetyl-O^6-(diphenylcarbamoyl)guanine (**G^{Pac}**) was silylated with BSA in dry ethylene chloride before all volatile reagents were removed in vacuum. Silylated **G^{Pac}** was dissolved in dry toluene and the coupling with **3a** was conducted in the presence of TMSOTf at 80°C for 1 hour to afford the nucleoside **4G^{Pac}** in 50% yield as a single N^9-regioisomer.

The protecting groups were easily removed from the nucleobase moiety by treatment of **4G^{Pac}** with ammonium hydroxide in methanol at room temperature to give compound **5G(Piv)** in 80% yield (Scheme 4). To attain **5G** we heated **4G^{Pac}** with ammonium hydroxide in methanol at 70°C. However, in contrast to the deprotection of **4,** after 7 days of heating we obtained the **5G** and **5G(Piv)** mixture, in which the former nucleoside was the minor component.

1D and 2D NMR Spectra

The structure of **4** and **5** was determined mostly on the basis of 1D and 2D NMR spectra. The *N*-1 linkage of the pyrimidine derivatives was evident, but that of **4T** was additionally proved by ^{1}H–^{1}H ROESY correlations; the H-1′ → H-6 interaction is shown in Figure 2.

An interesting feature in the ^{1}H NMR spectrum of **5C** is the existence of two broad N-H singlets at 7.15 and 7.24 ppm. This phenomenon is probably caused by the existence of **5C** as the imino(4)-keto(2) tautomer, but not the amino(4)-keto(2) one.[12] The elucidation of this problem would require additional experiments.

The *N*-9 and *N*-7 isomers of the adenine aza-nucleosides **5A^{9}** and **5A^{7}** can be readily distinguished based on the ^{1}H-^{13}C HMBC correlations, which

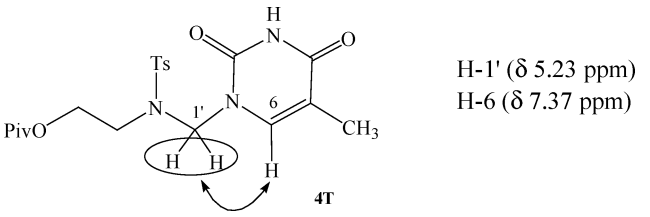
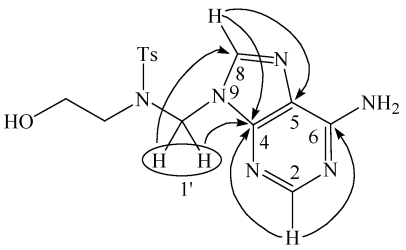
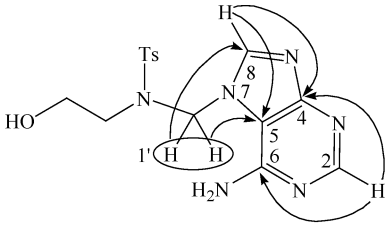


FIGURE 2 The principal ^{1}H-^{1}H ROESY correlations observed in the spectrum of **4T**.



5A^9

H (ppm)	C (ppm)
H–1' (5.67)	C–4 (149.31)
H–2 (8.11)	C–5 (118.30)
H–8 (8.06)	C–6 (155.96)
	C–8 (140.70)



5A^7

H (ppm)	C (ppm)
H–1' (5.58)	C–4 (160.27)
H–2 (8.22)	C–5 (110.30)
H–8 (8.31)	C–6 (151.38)
	C–8 (146.01)

FIGURE 3 The principal ^{1}H-^{13}C HMBC correlations observed in the spectra of **5A^9** and **5A^7**.

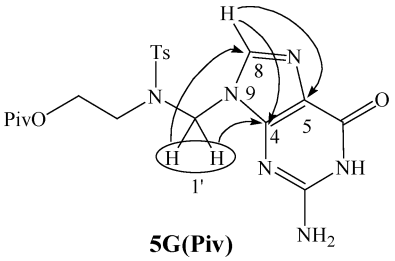
are shown in Figure 3. The N^9-linkage in **5A^9** was proved by H−1′ → C-4 HMBC correlation and the N^7-one in **5A^7** by the H-1′ → C–5 interaction.[13]

The *N*-9 alkylation pattern at guanine derivative **5G(Piv)** was proved by H-1′ → C-4 HMBC correlation (Figure 4).[13]

Antiviral Activity

The compounds **4T**, **5** (**T, C, FU, A^9, A^7, G(Piv),** and **G**) were evaluated in vitro against a variety of viruses in different host cell cultures:

(a) Vero cell cultures: parainfluenza-3 virus, reovirus-1, Sindbis virus, Coxsackie B4 virus and Punta Toro virus;
(b) E_6SM cell cultures: herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), herpes simplex virus-1 (TK − KOS ACV^r), vaccinia virus and vesicular stomatitis virus;
(c) HeLa cell cultures: vesicular stomatitis virus, Coxsackie B4 virus and respiratory syncytial virus.



5G(Piv)

H (ppm)	C (ppm)
H–1' (5.47)	C–4 (151.01)
H–8 (7.52)	C–5 (116.09)
	C–8 (136.90)

FIGURE 4 The principal ^{1}H-^{13}C HMBC correlations observed in the spectrum of **5G(Piv)**.

Brivudin, (*S*)-9-(2,3-Dihydroxypropyl)adenine, *Ribavirin*, *Acyclovir*, and *Ganciclovir* were used as the reference compounds. The following minimum cytotoxic concentration values[14] were estimated for tested azanucleosides: (*i*) Vero cell cultures: 200 μM for all compounds; (*ii*) E_6SM cell cultures: >200 μM for **4T** and **5** (**T, C, FU, A^9, A^7** and **G**); (*iii*) HeLa cell cultures: >200 μM for **4T** and **5** (**T, C, FU, A^9, A^7** and **G**); (*iv*) E_6SM or HeLa cell cultures: 200 μM or 40 μM for compound **G(Piv)**; respectively.[15] No specific antiviral effects were noted for any of the compounds against any of the viruses evaluated.

EXPERIMENTAL

General

Acetonitrile and dimethylformamide were dried prior to use according to known procedures. Reagent and solvents were obtained from Sigma-Aldrich, Poland. High resolution mass spectra (Electrospray Ionisation, ESI) were performed at Laboratory of Mass Spectrometry, Institute of Organic Chemistry, Polish Academy of Science (Warsaw) on Mariner spectrometer in positive ionization mode (samples were loop injected in methanol solution). The IR spectra were recorded at Division of Organic Chemistry, Faculty of Chemistry, Warsaw University of Technology, on a Specord M80 (Carl-Zeiss Jena) spectrometer in KBr disc; absorption maxima (ν_{max}) are given in cm^{-1}. Elemental analyses were performed at Department of Analytical Chemistry, Warsaw University of Technology, on a Perkin Elmer 2400 apparatus. ^{1}H- and ^{13}C-NMR spectra of all compounds were recorded at Division of Organic Chemistry, Faculty of Chemistry, Warsaw University of Technology, on a Varian Gemini 200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50 MHz). ^{1}H and ^{13}C chemical shifts are reported in ppm relative to the solvent signals: $CDCl_3$, δ_H(residual $CHCl_3$) 7.26 ppm, δ_C 77.16 ppm or DMSO-d_6, δ_H(residual DMSO) 2.50 ppm, δ_C 39.52 ppm; signals are quoted as "s" (singlet), "d" (doublet), "t" (triplet), "dt" (doublet of triplets), "m" (multiplet), and "sbr" (broad singlet). Coupling constants *J* are reported in Hz. ^{1}H-^{13}C HMBC (**H**eteronuclear **M**ultiple **B**ond **C**orrelation) and ^{1}H–^{1}H ROESY (**R**otational nuclear **O**verhauser **E**ffect **S**pectroscop**Y**) spectra were measured at Division of Homogenous Catalysis and Organometallic Chemistry, Faculty of Chemistry, Warsaw University of Technology, on a Varian Gemini 400 spectrometer in DMSO-d_6. Precoated Merck silica gel 60 F_{254} (0.2 mm) plates were used for thin-layer chromatography (TLC), and the spots were detected under UV light (254 nm). Column chromatography was performed using silica gel (200−400 mesh) purchased from Merck Ltd. (Poland).

The anhydrous $MgSO_4$ was employed as a drying agent. Solvents were distilled off under reduced pressure on the rotating evaporator.

***p*-Toluenesulfonamides** (**2**). A mixture of *N*-(2-hydroxyethyl)-*p*-toluenesulfonamide **1**[8] (5 g, 23 mmol), acid chloride (25 mmol) and pyridine (10 cm^3) was kept at room temperature for 1 day. The mixture was diluted with water (20 cm^3) and then chloroform (60 cm^3) was added. After 1 hour stirring organic layer was separated, washed subsequently with water, 10% HCl aq (3 × 20 cm^3), water and dried. Solvent was distilled off to give **2a** or **2b**.

***N*-(2-Pivaloyloxyethyl)-*p*-toluenesulfonamide** (**2a**). Yield 90% (6.3 g, crude), mp 54–56°C. The crude product was used in the next step without purification. An analytical sample was crystallized from hexane-ethyl acetate mixture (1/1, v/v). δ_H ($CDCl_3$) 1.15 (9H, s) 2.42 (3H, s), 3.22 (2H, dt, $^3J_{H\text{-}H} = 6.0$, $^3J_{H\text{-}H} = 5.2$), 4.07 (2H, t, $^3J_{H\text{-}H} = 5.2$), 4.96 (1H, t, $^3J_{H\text{-}H} = 6.0$, NH), 7.30 (2H, m), 7.74 (2H, m). δ_C ($CDCl_3$) 21.65, 27.22, 38.89, 42.52, 62.82, 127.16, 129.96, 137.03, 143.82, 178.53; ν_{max} 3304, 2976, 1720, 1324, 1156, 1284; HRMS m/z calcd for $C_{14}H_{21}NO_4NaS$ 322.1084 $(M+Na)^+$. Found: 322.1098.

***N*-(2-Benzoyloxyethyl)-*p*-toluenesulfonamide** (**2b**). 6.7 g (91%), mp. 107–109°C [hexane-ethyl acetate mixture (1/1, v/v)]. δ_H ($CDCl_3$) 2.37 (3H, s, CH_3), 3.37 (2H, dt, $^3J_{H\text{-}H} = 6.0$, $^3J_{H\text{-}H} = 5.0$), 4.33 (2H, t, $^3J_{H\text{-}H} = 5.0$), 5.20 (1H, t, $^3J_{H\text{-}H} = 6.0$, NH), 7.23 (m, 2H), 7.40 (m, 2H), 7.56 (m, 1H), 7.74 (m, 2H), 7.94 (m, 2H). δ_C ($CDCl_3$) 21.66, 42.56, 63.49, 127.15, 128.56, 129.52, 129.81, 129.94, 133.47, 136.98, 143.78, 166.48; ν_{max} 3272, 1700, 1288. Anal. calcd for $C_{16}H_{17}NO_4S$: C 60.17, H 5.37, N 4.39. Found: C 60.19, H 5.35, N 4.40.

***N*-(Pivaloyloxymethyl)sulfonamides** (**3**). Chloromethyl pivalate (2.26 g, 15 mmol, 2.16 cm^3) was added to a stirred mixture of *p*-toluenesulfonamide **2** (5 mmol), anhydrous potassium carbonate (2.77 g, 20 mmol) and dry DMF (3 cm^3). The mixture was left at room temperature for 5 days and then was poured into ice-cold water (10 cm^3). **1** was extracted with methylene chloride (3 × 10 cm^3). The extracts combined were washed with water and dried. Solvent was distilled off to give **3a** or **3b**.

***N*-(2-Pivaloyloxyethyl)-*N*-(pivaloyloxymethyl)-*p*-toluenesulfonamide** (**3a**). Yield 85% (1.75 g, crude), mp 49–52°C. An analytical sample was crystallized form hexane. δ_H ($CDCl_3$) 0.99 (9H, s), 1.21 (9H, s), 2.42 (3H, s), 3.44 (2H, t, $^3J_{H\text{-}H} = 5.6$), 4.24 (2H, t, $^3J_{H\text{-}H} = 5.6$), 5.54 (2H, s), 7.29 (2H, m), 7.75 (2H, m). δ_C ($CDCl_3$) 21.60, 26.86, 27.27, 38.84, 45.35, 62.55, 72.38, 127.68, 129.83, 137.07, 144.05, 178.03, 178.37; ν_{max} 2924, 1728, 1464, 1384, 1156. Anal. calcd for $C_{20}H_{31}NO_6S$: C 58.09, H 7.56, N 3.39. Found C 57.96, H 7.51, N 3.43.

***N*-(2-Benzoyloxyethyl)-*N*-(pivaloyloxymethyl)-*p*-toluenesulfonamide** (**3b**). Yield 80% (1.86 g, crude), mp 67–70°C. An analytical sample was crystallized form hexane. δ_H ($CDCl_3$) 1.00 (9H, s), 2.40 (3H, s), 3.60 (2H, t, $^3J_{H\text{-}H} = 5.6$), 4.50 (2H, t, $^3J_{H\text{-}H} = 5.6$), 5.60 (2H, s), 7.32–7.67 (5H, m), 7.77 (2H, m), 8.02 (2H, m). δ_C ($CDCl_3$) 21.62, 26.89, 38.84, 45.52, 62.99,

72.48, 127.73, 128.56, 129.84, 133.32, 137.01, 144.09, 166.38, 178.07; ν_{max} 2976, 1720, 1732, 1452, 1268. Anal. calcd for $C_{22}H_{27}NO_6S$: C 60.95, H 6.28, N 3.23. Found: C 61.01, H 6.26, N 3.31.

General procedure for the coupling of pyrimidine nucleobases and N^6-benzoyladenine with 3. Nucleobase, BSA, Lewis acid and **3** were used in the following molar ratios: (i) 2.0/4.0/1.66/1.0 for the preparation of **4C^{Bz}**, **4′C^{Bz},** and **4T**, (ii) 2.0/4.0/3.0/1.0 for the preparation of **4FU** and **4A^9/4A^7**. TMSOTf was used as Lewis acid for all couplings except for the reaction with **A^{Bz}** where $SnCl_4$ was employed. The mixture of nucleobase (2.0 mmol), BSA (814 mg, 4 mmol, 1 cm^3), and dry acetonitrile (10 cm^3) was stirred at room temperature under an argon atmosphere for 1 hour. Then the solution of **3** (1.0 mmol) in dry acetonitrile (1 cm^3) and Lewis acid (in an amount depending on the kind of base) were added successively. The reaction mixture was left at room temperature for 3 days, then ethyl acetate (50 cm^3) and saturated solution of sodium bicarbonate (1 cm^3) were added successively and the resulting mixture was stirred for 1 hour. The mixture was filtered through a Celite pad. The organic phase was separated, washed with water, brine, and dried. The solvent was distilled off. Crude **4** was purified by flash chromatography.

4-(Benzoylamino)-1-[*N*-(2-benzoyloxyethyl)-*p*-toluenesulfonylaminomethyl]-1*H*-pyrimidin-2-one (**4′C^{Bz}**). Yield 25% (contaminated with pivalic acid, ca. 20 mol%) (chloroform-acetone, 85/15, v/v). δ_H ($CDCl_3$) 1.22 (9H, s, pivalic acid), 2.27 (3H, s, CH_3) 3.85 (2H, t, $^3J_{H\text{-}H}$ = 5.4, H-3′), 4.48 (2H, t, $^3J_{H\text{-}H}$ = 5.4, H-4′), 5.48 (2H, s, H-1′), 7.14 (1H, d, $^3J_{H\text{-}H}$ = 7.4, H-5), 7.30–7.61 (10H, m, Ph), 7.85–7.98 (4H, m, Ph), 8.04 (2H, m, Ph), 8.07 (1H, d, $^3J_{H\text{-}H}$ = 7.4, H-6). δ_C ($CDCl_3$) 21.50 (CH_3), 27.12 (pivalic acid), 38.47 (pivalic acid), 48.07, 61.81, 62.64, 97.55, 126.86, 128.17, 128.32, 128.77, 129.65, 130.02, 132.81, 133.06, 133.21, 136.26, 144.35, 148.75, 155.78 163.53, 167.10, 184.01 (pivalic acid). ν_{max} 3382, 1620, 1520; HRMS m/z calcd for $C_{28}H_{26}N_4O_6NaS$ $(M+Na)^+$ 569.1465. Found: 569.1496.

4-(Benzoylamino)-1-[*N*-(2-pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-1*H*-pyrimidin-2-one (**4C^{Bz}**). Yield 64% (methylene chloride–methanol, 99/1, v/v), mp 151–156°C. δ_H ($CDCl_3$) 1.17 [9H, s, ($\underline{CH_3}$)$_3$C-], 2.39 (3H, s), 3.77 (2H, t, $^3J_{H\text{-}H}$ = 5.4, H-3′), 4.19 (2H, t, $^3J_{H\text{-}H}$ = 5.4, H-4′), 5.42 (2H, s, H-1′), 7.28 (1H, d, $^3J_{H\text{-}H}$ = 7.4, H-5), 7.49–7.63 (7H, m, Ph), 7.90 (2H, m, Ph), 8.05 (1H, d, $^3J_{H\text{-}H}$ = 7.4, H-6), 8.73 (1H, s, NH). δ_C ($CDCl_3$) 21.66, 27.30, 38.81, 48.35, 62.40, 62.52, 97.18, 126.88, 127.73, 129.21, 130.19, 133.48, 136.67, 144.49, 148.70, 162.91; 178.22. ν_{max} 3064, 2972, 1728, 1668, 1628, 1556, 1484, 1368, 1324, 1256, 1156; Anal. Calcd for $C_{26}H_{30}N_4O_6S$: C 59.30, H 5.74, N 10.64. Found C 59.14, H 5.70, N 9.81.

1-[*N*-(2-Pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-5-methyl-1*H*, 3*H*-pyrimidin-2,4-dione (**4T**). 67% (methylene chloride–methanol, 97/3, v/v), mp 145–149°C. δ_H ($CDCl_3$) 1.15 [9H, s, ($\underline{CH_3}$)$_3$C-], 1.89 (3H, d, $^4J_{H\text{-}H}$ = 1.4, CH_3), 2.41 (3H, s, CH_3), 3.65 (2H, t, $^3J_{H\text{-}H}$ = 5.6, H-3′), 4.15

(2H, t, $^3J_{H\text{-}H} = 5.6$, H-4′), 5.23 (2H, s, H-1′), 7.29 (2H, m, Ph), 7.37 (1H, q, $^4J_{H\text{-}H} = 1.4$, H-6), 7.62 (2H, m, Ph), 9.39 (1H, s, NH). δ_C ($CDCl_3$) 12.38, 21.60, 27.20, 38.74, 47.58, 60.43, 62.12, 111.45, 126.83, 130.12, 136.88, 139.60, 144.53, 151.55, 164.38, 178.15. ν_{max} 3340, 1724, 1656, 1500, 1322, 1152. Anal. calcd for $C_{20}H_{27}N_3O_6S$: C 54.90, H 6.22, N 9.60. Found: C 54.62, H 6.18, N 9.47.

1-[*N*-(2-Pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-5-fluoro-1*H*, 3*H*-pyrimidin-2,4-dione (**4FU**). 78% (hexane-ethyl acetate, 1/1, v/v), mp 170–179°C. δ_H ($CDCl_3$) 1.16 [9H, s, ($\underline{CH_3}$)$_3$C-], 2.44 (3H, s, CH_3) 3.64 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-3′), 4.14 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-4′), 5.24 (2H, s, H-1′), 7.33 (2H, m, Ph), 7.66 (2H, m, Ph), 7.76 (1H, d, $^3J_{H\text{-}F} = 5.6$), 8.86 (1H, s, NH). δ_C (DMSO-d_6) 20.96, 26.78, 38.81, 47.91, 60.98, 61.73, 126.71, 128.69 (d, $^2J_{C\text{-}F} = 33.4$), 136.55, 139.23 (d, $^1J_{C\text{-}F} = 221.0$), 143.94, 149.79, 157.13 (d, $^2J_{C\text{-}F} = 26.2$), 177.16. ν_{max} 3220, 1718, 1693, 1343, 1162, 1088. Anal. calcd for $C_{19}H_{24}FN_3O_6S$ C 51.69, H 5.48, N 9.52. Found: C 51.19, H 5.23, N 9.20.

6-(Benzoylamino)-9-[*N*-(2-pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-9*H*-purine (**4A^{Bz,9}**). Yield 31% (the second run 23%) (methylene chloride-acetone, 98/2, v/v), mp 45–49°C. δ_H ($CDCl_3$) 1.14 [9H, s, ($\underline{CH_3}$)$_3$C-], 2.31 (3H, s, CH_3), 3.71 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-3′), 4.21 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-4′), 5.77 (2H, s, H-1′), 7.13–7.51 (9H, m, Ph), 7.97 (2H, m, Ph), 8.20 (1H, s), 8.64 (1H, s), 9.32 (1H, s, NH). δ_C ($CDCl_3$) 21.50, 27.16, 38.72, 47.01, 55.71, 62.07, 122.47, 126.67, 127.93, 128.84, 129.95, 132.83, 133.56, 136.41, 143.37, 144.42, 149.61, 152.03, 152.87, 164.79, 178.13. ν_{max} 3408, 1620, 1520. HRMS m/z calcd for $C_{27}H_{31}N_6O_5S$ 551.2071 $(M+H)^+$. Found 551.2067.

6-(Benzoylamino)-7-[*N*-(2-pivaloyloxy-ethyl)-*p*-toluenesulfonylaminomethyl]-7*H*-purine (**4A^{Bz,7}**). Yield 23% (the second run 34%) (methylene chloride-acetone, 98/2, v/v), mp 72–74°C. HRMS m/z calcd for $C_{27}H_{30}N_6O_5NaS$ 573.1891 $(M+Na)^+$. Found 573.1903. Signals in ^{1}H– and ^{13}C–NMR spectra were broad, so their interpretation was impossible.

The rearrangement of 4A^{Bz,7}. The mixture of **4A^{Bz,7}** (50 mg, 0.1 mmol), TMSOTf (38 mg, 31 μl, 0.17 mmol) and toluene (20 cm^3) was heated in sealed tube at 80°C for 2 hours. Ethyl acetate (10 cm^3) and saturated solution of sodium bicarbonate (1 cm^3) were added successively and the resulting mixture was stirred for 1 hour. The mixture was filtered through a Celite pad. The organic phase was separated, washed with water, brine, and dried. The solvent was distilled off. The residue was purified by flash chromatography (methylene chloride-acetone, 98/2, v/v) to give **4A^{Bz,9}** (8 mg, 16%), mp 44–49°C. The ^{1}H– and ^{13}C–NMR spectra were consistent with those determined previously.

2-(Acetylamino)-6-(diphenylcarbamoyl)-9-[*N*-(2-pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-9*H*-purine (**4G^{Pac}**). The mixture of **G^{Pac}** (680 mg, 2 mmol), BSA (814 mg, 4 mmol, 1 cm^3) and dry ethylene chloride (10 cm^3) was heated at 80°C under an argon atmosphere in a sealed tube for

15 minutes. The solvent and BSA were removed in vacuum and the residue was dissolved in dry toluene (20 cm^3). Compound **3a** (413 mg, 1.0 mmol) in dry toluene (1 cm^3) and TMSOTf (378 mg, 310 μl, 1.7 mmol) were added to this solution, successively. The reaction mixture was heated at 80°C for 1 hour. Ethyl acetate (50 cm^3) and saturated solution of sodium bicarbonate (1 cm^3) were added to reaction mixture cooled to room temperature. The resulting mixture was stirred for 1 hour at room temperature. The mixture was filtered through a Celite pad. The organic phase was separated from the filtrate and washed with water, brine, and dried. The solvent was distilled off. **4G^{Pac}** was purified by flash chromatography (chloroform–acetone, 95/5, v/v). Yield 50%, mp 64–67°C. δ_H ($CDCl_3$) 1.13 [9H, s, ($\underline{CH_3}$)$_3$C-], 2.23 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.75 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-3′), 4.25 (2H, t, $^3J_{H\text{-}H} = 5.6$, H-4′), 5.59 (2H, s, H-1′) 7.05–7.43 (14H, m, Ph), 8.07 (1H, s, H-8), 8.65 (1H, s, NH). δ_C ($CDCl_3$) 21.30, 24.96, 27.10, 38.65, 47.32, 55.92, 61.96, 120.28, 126.49, 126.95, 129.16, 129.77, 136.24, 141.64, 144.25, 150.23, 152.17, 154.87, 155.98, 169.73, 178.25. ν_{max} 2928, 1721, 1334, 759, 736.

Procedure for a deprotection of 4. The mixture of **4** (1.0 mmol), conc. NH_3 aq (2 cm^3) and MeOH (4 cm^3) was heated in a sealed tube at 70°C for 3–7 days (for details see Schemes 2–4) till a substrate was not detected (TLC). Then solvent was distilled off and a residue was purified by flash chromatography.

4-Amino-1-[*N*-(2-hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-1*H*-pyrimidin-2-one (**5C**). Yield 65% (chloroform–methanol, 9/1, v/v), mp 131–139°C. δ_H (DMSO-d_6) 2.39 (3H, s, CH_3) 3.41 (4H, m, H-3′, H-4′), 4.77 (1H, sbr, OH), 5.14 (2H, s, H-1′), 5.69 (1H, d, $^3J_{H\text{-}H} = 7.7$, H-5), 7.15 (1H, sbr, NH), 7.24 (1H, sbr, NH), 7.37 (2H, m, Ph), 7.57 (2H, d, $^3J_{H\text{-}H} = 7.7$, H-6), 7.77 (2H, m, Ph). δ_C (DMSO-d_6) 20.96, 50.49, 59.61, 61.51, 93.92, 126.74, 129.20, 129.76, 136.78, 143.43, 145.23, 155.85, 166.04; ν_{max} 3336, 2928, 1664, 1640, 1500, 1332, 1152. HRMS m/z calcd for $C_{14}H_{19}N_4O_4S$: $(M+H)^+$ 339.1122. Found: 339.1138.

1-[*N*-(2-Hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (**5T**). Yield 64% (chloroform–methanol, 98/2, v/v), mp 204–206°C. δ_H (DMSO-d_6) 1.73 (3H, s, CH_3), 2.38 (3H, s, CH_3), 3.37 (2H, m, H-3′), 3.45 (2H, m, H-4′), 4.81 (1H, m, OH), 5.15 (1H, s, H-1′), 7.38 (3H, m, H-6, Ph), 7.69 (2H, m, Ph), 11.26 (1H, sbr, NH). δ_C (DMSO-d_6) 11.96, 20.96, 50.85, 59.77, 60.51, 108.76, 126.71, 129.77, 136.81, 140.09, 143.57, 151.07, 163.94; ν_{max} 3405, 3029, 1718, 1695, 1439, 1340, 1278, 1160, 1136. Anal. calcd for $C_{15}H_{19}N_3O_5S$: C 50.98, H 5.42, N 11.98. Found: C 50.84, H 5.27, N 11.64.

1-[*N*-(2-Hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (**5FU**). Yield 63% (chloroform-acetone, 85/15, v/v), mp 196–202°C. δ_H (DMSO-d_6) 2.39 (3H, s, CH_3), 3.40 (4H, m, H-3′, H-4′), 4.85 (1H, sbr, OH), 5.14 (2H, s, H-1′), 7.41 (2H, m, Ph), 7.72 (2H, m,

Ph), 7.91 (1H, d, $^3J_{H\text{-}F} = 5.6$), 11.75 (1H, sbr, NH). δ_C (DMSO-d_6) 20.96, 51.19, 59.75, 61.12, 126.78, 128.76 (d, $^2J_{C\text{-}F} = 34.15$), 129.85, 136.52, 139.29 (d, $^1J_{C\text{-}F} = 229.10$), 143.74, 149.70, 157.24 (d, $^2J_{C\text{-}F} = 25.75$). ν_{max} 3432, 2999, 2850, 1741, 1727, 1699, 1664, 1447, 1336, 1156, 1138. Anal. calcd for $C_{14}H_{16}FN_3O_5S$: C 47.05, H 4.51, N 11.76. Found: C 47.01, H 4.43, N 11.62.

6-Amino-9-[*N*-(2-hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-9*H*-purine (**5A**[9]). Yield 65% (chloroform-methanol, 99/1, v/v), mp 210–215°C. δ_H (DMSO-d_6) 2.39 (3H, s, CH_3), 3.49 (4H, m), 4.98 (1H, sbr, OH), 5.67 (2H, s, H-1′), 7.27 (4H, m, Ph, NH_2), 7.58 (2H, m, Ph), 8.06 (1H, s, H-8), 8.11 (1H, s, H-2). δ_C (DMSO-d_6) 20.92 (CH_3), 50.26 (C-3′), 55.98 (C-1′), 59.59 (C-4′), 118.30 (C-5), 126.61 (C_{arom}-H), 129.57 (C_{arom}-H), 136.47 (C_{arom}), 140.70 (C–8), 143.48 (C_{arom}), 149.31 (C–4), 152.67 (C-2), 155.96 (C–6). ν_{max} 3441, 1656, 1375, 1150. HRMS m/z calcd for $C_{15}H_{19}N_6O_3S$ $(M+H)^+$ 363.1234. Found: 363.1216.

6-Amino-7-[*N*-(2-hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-7*H*-purine (**5A**[7]). Yield 76% (chloroform-methanol, 99/1, v/v), mp 226–231°C. δ_H (DMSO-d_6) 2.42 (3H, s, CH_3), 3.07 (2H, m, H-3′), 3.19 (2H, m, H-4′), 4.79 (1H, sbr, OH), 5.83 (2H, s, H-1′), 7.00 (2H, s, NH_2), 7.46 (2H, m, Ph), 7.78 (2H, m, Ph), 8.22 (1H, s, H-2), 8.31 (1H, s, H-8). δ_C (DMSO-d_6) 21.00 (CH_3), 49.00 (C-3′), 59.67 (C-4′), 60.34 (C-1′), 110.30 (C-5), 126.97 (C_{arom}-H), 130.15 (C_{arom}-H), 135.13 (C_{arom}), 144.25 (C_{arom}), 146.01 (C-8), 151.38 (C-6), 152.70 (C-2), 160.27 (C-4). ν_{max} 3199, 3096, 2874, 1655,. HRMS m/z calcd for $C_{15}H_{18}N_6O_3NaS$ $(M+Na)^+$ 385.1059. Found: 385.1064.

2-Amino-9-[*N*-(2-pivaloyloxyethyl)-*p*-toluenesulfonylaminomethyl]-9*H*-purin-6-one [**5G(Piv)**] Yield 80% (chloroform-methanol, 95/5, v/v), mp 230°C (dec), δ_H (DMSO-d_6) 1.09 [9H, s, $(\underline{CH_3})_3C$-], 2.35 (3H, s, CH_3), 3.68 (2H, t, $^3J_{H\text{–}H} = 4.8$, H-3′), 4.18 (2H, t, $^3J_{H\text{–}H} = 4.8$, H-4′), 5.47 (2H, s, H-1′), 6.41 (2H, sbr, NH_2), 7.31 (2H, m, Ph), 7.52 (1H, s, H-8), 7.59 (2H, m, Ph), 10.53 (1H, sbr, NH). δ_C (DMSO-d_6) 20.89 (CH_3), 26.79 [$(\underline{CH_3})_3C$], 37.95 [$(CH_3)_3\underline{C}$], 46.80 (C-3′), 54.92 (C-1′), 61.49 (C-4′), 116.09 (C-5), 126.57 (C_{arom}-H), 129.63 (C_{arom}-H), 136.39 (C_{arom}), 136.90 (C-8), 143.53 (C_{arom}), 151.01 (C-4), 153.63 [C-2(6)], 156.53 [C-6(2)], 177.28 (C=O). ν_{max} 2928, 1721, 1334, 759, 736. HRMS m/z calcd for $C_{20}H_{26}N_6O_5NaS$ $(M+Na)^+$ 485.1578. Found: 485.1600.

2-Amino-9-[*N*-(2-hydroxyethyl)-*p*-toluenesulfonylaminomethyl]-9*H*-purin-6-one (5G). Yield 9% (chloroform-methanol, 95/5, v/v). δ_H (DMSO-d_6) 2.36 (3H, s, CH_3), 3.40 (4H, m, H-3′, H-4′), 4.84 (1H, sbr, OH), 5.46 (2H, s, H−1′), 6.45 (2H, sbr, NH_2), 7.32 (2H, m, Ph), 7.60 (3H, m, Ph, H-8), 10.68 (1H, sbr, NH). δ_C (DMSO-d_6) 20.95, 49.78, 55.48, 59.62, 116.13, 126.73, 129.62, 136.52, 137.04, 143.43, 151.10, 153.71, 156.70. HRMS m/z calcd for $C_{15}H_{18}N_6O_4NaS$ $(M+Na)^+$ 401.1002. Found: 401.0985.

REFERENCES

1. De Clercq, E. Antiviral drugs in current clinical use. *J. Clin. Virol.* **2004**, 30, 115–133.
2. Galmarini, C.M.; Mackey, J.R.; Dumontet, C. Nucleoside analogues and nucleobases in cancer treatment. *Lancet Oncol.* **2002**, 3, 415–424.
3. De Clercq, E.; Field, H.J. Antiviral prodrugs–The development of successful prodrug strategies for antiviral chemotherapy. *Br. J. Pharmacol.* **2006**, 147, 1–11.
4. Selected papers published during last five years: (a) Gao, H.; Mitra, A.K. Regioselective synthesis of various prodrugs of ganciclovir. *Tetrahedron Lett.* **2000**, 41, 1131–1136; (b) Beadle, J.R.; Kini, G.D.; Aldern, K.A.; Gardner, M.F.; Wright, K.N.; Rybak, R.J.; Kern, E.R.; Hostetler, K.Y. Synthesis and antiviral evaluation of 1-O-hexadecylpropanediol-3-P-acyclovir: Efficacy against HSV-1 infection in mice. *Nucleosides, Nucleotides Nucleic Acids* **2000**, 19, 471–479; (c) McGuigan, C.; Slater, M.J.; Parry, N.R.; Perry, A.; Harris, S. Synthesis and antiviral activity of acyclovir-5′-(phenylmethoxyalaninyl)phosphate as a possible membrane-soluble nucleotide prodrug. *Bioorg. Med. Chem. Lett.* **2000**, 10, 645–647; (d) Balzarini, J.; Haller-Meier, F., De Clercq, E.; Meier C. Antiviral activity of cyclosaligenyl prodrugs of acyclovir, carbovir and abacavir. *Antiviral Chem. Chemother.*, **2001**, 12, 301–306; (e) Tak, R.V.; Pal, D.; Gao, H.; Dey, S.; Mitra, A.K. Transport of acyclovir ester prodrugs through rabbit cornea and SIRC-rabbit corneal epithelial cell line. *J. Pharm. Sci.* **2001**, 90, 1505–1515; (f) Gao, H.; Mitra, A.K. Regioselective synthesis of acyclovir and its various prodrugs. *Synth. Commun.* **2001**, 31, 1399–1420; (g) Yang, C.; Gao, H.; Mitra, A.K. Chemical stability, enzymatic hydrolysis, and nasal uptake of amino acid ester prodrugs of acyclovir. *J. Pharm. Sci.* **2001**, 90, 617–624; (h) Dias, C.S.; Anand, B.S.; Mitra, A.K. Effect of mono- and di-acylation on the ocular disposition of ganciclovir: Physicochemical properties, ocular bioreversion, and antiviral activity of short chain ester prodrugs. *J. Pharm. Sci.* **2002**, 91, 660–668; (i) Nashed, Y.E.; Mitra, A.K. Synthesis and characterization of novel dipeptide ester prodrugs of acyclovir. *Spectrochim. Acta A* **2003**, 59, 2033–2039; (j) Salamonczyk, G.M. Acyclovir terminated thiophosphate dendrimers. *Tetrahedron Lett.* **2003**, 44, 7449–7453.
5. El Ashry, E.S.H.; El Kilany, Y. Acyclonucleosides: Part 1. *Seco*–Nucleosides. *Adv. Heterocycl. Chem.* **1997**, 67, 391–438, Acyclonucleosides: Part 2. dis*eco*–Nucleosides. *Adv. Heterocycl. Chem.* **1997**, 68, 1–88; Acyclonucleosides: Part 3. *tri*–, *tetra*–, and *pentaseco*–Nucleosides. *Adv. Heterocycl. Chem.* **1998**, 69, 129–215; (b) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Aspects.* Gorgon and Breach Science Publishers: Amsterdam, 2001; pp. 161–172; (c) Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis.* John Wiley: New York, 2001; Tables I-XI; pp. 110–589; (d) Ichikawa, E.; Kato. K. Sugar-modified nucleosides in past 10 years, A review. *Curr. Med. Chem.* **2001**, 8, 385–423; (c) Jeong, L.S.; Lee, J.A. Recent advances in the synthesis of the carbocyclic nucleosides as potential antiviral agents. *Antivir. Chem. Chemother*. **2004**, 15, 235–250; (e) Kumar, R. 5-(1-Substituted) alkyl pyrimidine nucleosides as antiviral (herpes) agents. *Curr. Med. Chem.* **2004**, 11, 2749–2766.
6. Montgomery, J.A.; Temple, C. Synthesis of potential anticancer agents. XXVI. The alkylation of 6-chloropurine. *J. Am. Chem. Soc.* **1961**, 83, 630–635; (b) Nishitani, T.; Horikawa, H.; Iwasaki, T.; Matsumoto, K.; Inoue, I.; Miyoshi, M. Synthetic electroorganic chemistry. 14. Synthesis of 5-fluorouracil derivatives having N-acylazacycloalkanes and lactams. *J. Org. Chem*. **1982**, 47, 1706–1712; (c) Sergeev, V.N.; Shapovalenko, E.P.; Baukov, Yu.I. Silyl method for the synthesis of N-(organosulfonamidomethyl)lactams and imides. *Russ. J. Gen. Chem*. (Engl. Transl.) **1987**, 57, 1177–1182 [*Zh. Obshch. Khim.*, **1987**, 57, 1315–1321]; (d) Nishitani, T.; Iwasaki, T.; Mushika, Y.; Inoue, I.; Miyoshi, M. Synthesis of 3-amino-3-(5-fluorouracil-1-yl)propionic acid and 4-amino-4-(5-fluorouracil-1-yl)butyric acid derivatives. *Chem. Pharm. Bull*. **1980**, 28, 1137–1141; (e) Inoue, K.; Iwasaki, T.; Nishitani, T.; Kondou, K.; Arai, Y. 5-Fluorouracil derivative and its preparation. JP58216169, **1983** (*Chem. Abstr.* **1984**, 100, 174851b); (f) Miyoshi, S; Inoue, K.; Mushishika, Y.; Iwasaki T.; Nishitani, T.; Arai, Y. 5-Fluorouracil derivative and preparation thereof. JP58213762, **1983** (*Chem. Abstr.* **1984**, 100, 174852c); (g) Kingsbury, W.D.; Boehm, J.C.; Mehta, R.J.; Grappel, S.F.; Gilvarg, C. A novel peptide delivery system involving peptidase activated prodrugs as antimicrobial agents. Synthesis and biological activity of peptidyl derivatives of 5-fluorouracil. *J. Med. Chem.* **1984**, 27, 1447–1451; (h) Nichifor, M.; Schacht, E.H. Synthesis of peptide derivatives of 5-fluorouracil. *Tetrahedron* **1994**, 50, 3747–3760; (i) Khutova, B.M.; Klyuchko, S.V.; Prikazchikova, L.P. Amidoalkylation of pyrimidine bases of nucleic acids. *Chem. Heterocycl. Compd.* (Engl. Transl.) **1991**, 27, 407–409 [*Khim. Geterotsikl. Soedin*. **1991**, 512–515]; (j) Besova, E.A.; Goloshchapov, N.M.; Goloshchapova, E.N.; Michurina, A. E.; Shipov, A. G.; Baukov, Yu. I. Reaction of Substituted 5-oxazolidinones with

2,4-bis(trimethylsiloxy)pyrimidines. *Russ. J. Gen. Chem.* (Engl. Transl.) **1998**, 68, 469–471 [*Zh. Obshch. Khim.*, **1998**, 68, 502–504]; (k) Madec-Lougerstay, R.; Florent, J.-C.; Monneret, C. Synthesis of self-immolative glucuronide spacers based on aminomethylcarbamate. Application to 5-fluorouracil prodrugs for antibody-directed enzyme prodrug therapy. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1369–1376; (l) Kita, Y; Shibata, N; Yoshida, N; Tohjo, T. An efficient synthesis of 4-heterofunction-substituted 3-(1-hydroxy)ethylazetidin-2-ones from 3-(1-hydroxy)ethyl-4-phenylsulfinylazetidin-2-one by reaction with silylated heteronucleophiles. *Chem. Pharm. Bull*. **1992**, 40, 1733–1736; (m) Gilchrist, T.L; Mendonca, R. Addition of pyrimidine and purine bases to benzyl 2H-azirine-3-carboxylate. *Synlett* **2000**, 12, 1843–1845; (n) Zheltonogova, E.A.; Oleneva, G.I.; Shapovalenko, E.P.; Belavin, I.Yu.; Shipov, A.G.; Baukov, Yu.I. Silyl variant of the amidoalkylation of 5-substituted uracils with 2-pyrrolidinone derivatives. *Russ. J. Gen. Chem.* (Engl. Transl.) **1990**, 60, 1245–1249 [*Zh. Obshch. Khim.* **1990**, 60, 1390–1394]; (o) Bergmeier, S.C.; Fundy, S.L.; Drach, J.C. Synthesis and antiviral activity of novel aza-acyclonucleosides. *Nucleosides, Nucleotides Nucleic Acid* **1999**, 18, 227–238; (p) Sheikha, G.A.; La Colla, P.; Loi, A.G. A new class of acyclic nucleoside phosphonates: synthesis and biological activity of 9-{[(phosphonomethyl)aziridin-1-yl]methyl}guanine (pmamg) and analogues. *Nucleosides, Nucleotides Nucleic Acids* **2002**, 10, 619–635.

7. Koszytkowska-Stawinska, M.; Sas, W. Facile synthesis of acyclic azanucleosides from *N*-pivaloyloxymethyl amides and sulfonamides: synthesis of aza-analogues of Ganciclovir. *Tetrahedron Lett.* **2004**, 45, 5437–5440.
8. Augstein, J.; Austin, W.C.; Boscott, R.J.; Green, S.M.; Worting, C.R. Some Cardiovascular effects of a series of aryloxyalkylamines. I. *J. Med. Chem.* **1965**, 8, 356–367.
9. Vorbrüggen, H.; Ruh-Pohlenz, C. *Handbook of Nucleoside Synthesis*. John Wiley: New York, 2001, pp. 29–33 and 110–140.
10. Robins, M.J.; Zou, R.; Hansske, F.; Madej, D.; Tyrrell, D.L.J. Synthesis, transformation chemistry, and biological activity of guanine nucleosides and analogues. *Nucleosides, Nucleotides Nucleic Acids* **1989**, 8, 725–741.
11. (a) Zou, R.; Robins, M.J. High-yield regioselective synthesis of 9-glycosyl guanine nucleosides and analogues via coupling with 2-*N*-acetyl-6-*O*-diphenylcarbamoylguanine. *Can. J. Chem.* **1987**, 65, 1436–1437; (b) Robins, M.J.; Zou, R.; Guo, Z; Wnuk, S.F. Nucleic acid related compounds. 93. A solution for the historic problem of regioselective sugar-base coupling to produce 9-glycosylguanines or 7-glycosylguanines. *J. Org. Chem.* **1996**, 61, 9207–9212; (c) Tolle-Sander, S.; Lentz, K.A.; Maeda, D.Y.; Coop, A.; Polli, J. E. Increased acyclovir oral bioavailability via a bile acid conjugate. *Mol. Pharm.* **2004**, 1, 40–48.
12. Žinić, B.; Krizmanić, I.; Vikić-Topić, D.; Žinić, M. 5-Bromo- and 5–iodo-*N*-1-sulfonylated cytosine derivatives. Exclusive formation of keto-imino tautomers. *Croat. Chem. Acta* **1999**, 72, 957–966.
13. Marek, R.; Sklenar, V. NMR studies of purines. *Annu. Rep. NMR Spectrosc.* **2005**, 54, 201–242.
14. Required to cause a microscopically detectable alteration of normal cell morphology.
15. The minimum cytotoxic concentrations of reference compounds were as follows: *Brivudin* and *Ribavirin* (Vero, E_6SM or HeLa cells, >400 μM); (*S*)-9-(2,3-Dihydroxypropyl)adenine (Vero or HeLa cells, >400 M); *Acyclovir* (E_6SM cells, >400 μM), *Ganciclovir* (E_6SM cells, >100 μM).