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Synthesis of aza-analogues of *Ganciclovir*

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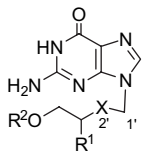
Abstract—Aza-analogues of *ganciclovir* have been prepared via coupling of nucleobases with *N*-[2-pivaloyloxy-1-(pivaloyloxymethyl)-ethyl]methanesulfonamide or 3-mesyl-4-(benzoyloxymethyl)-1,3-oxazolidine.

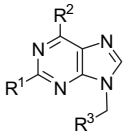
1. Introduction

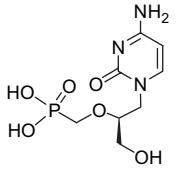
The synthesis of acyclic nucleosides[1,2] has attracted considerable attention due to their antiviral[3] or anticancer activity.[4] Some of them (Fig. 1) have been approved for the clinical treatment of herpes virus infections (e.g. *acyclovir*, *ganciclovir*, *penciclovir*, *cidofovir*, *famciclovir*) or hepatitis B virus infections (e.g. *adefovir*).[3] In order to improve their efficacy, the parent antiviral drugs are also used in the form of prodrugs, usually esters (e.g. *valacyclovir* or *valganciclovir*, Fig. 1).[5] The synthesis of new nucleoside analogues bearing molecular modifications on the sugar mimic is one of the approaches towards promising antiviral agents.[1] Some of these modifications involve replacement of the oxygen or carbon atom at the 2′-position with sulfur or nitrogen.[1a,6] Acyclic analogues with a nitrogen atom at the 2′-position (termed acyclic azanucleosides) are much less known than the corresponding oxa or carbo derivatives.[7]

Most of them are amino acid or peptide derivatives of 5-fluorouracil. They are obtained by the condensation of *N*-(α-acetyloxyalkyl)amides (which, are derivatives of amino acids or peptides) with the nucleobase or its silylated derivative in the presence of triethylamine (or sodium hydride)[6e,f,k] or tin(IV) chloride.[6d] The acyclic aza-analogues have also been synthesized by the coupling of silylated nucleobases, natural or synthetic, with *N*-(acetoxymethyl)amides,[6m] *N*-(chloromethyl)sulfonamides[6g] or *N*-(chloromethyl)amides.[6i] Other methods, such as Curtius rearrangement, have also been reported.[6a] Acyclic azanucleosides containing a nitrogen atom at the 3′-position are also known; they disclose biological activity.[8]

Recently we have shown that acyclic azanucleosides can be readily obtained by the coupling of *N*-(pivaloyloxymethyl)-amides or sulfonamides with silylated nucleobases in the presence of Lewis acids. Using this approach we have synthesized the aza-analogues of *ganciclovir*[9] and *acyclovir*[10] protected with mesyl or tosyl group, respectively, at a nitrogen atom of the sugar mimic.[11] Herein we describe two methods for the first synthesis of the aza-analogues of *ganciclovir*: (i) from *N*-[2-pivaloyloxy-1-







	X	R^1	R^2		R^1	R^2	R^3	
Acyclovir	O	H	H	*Adefovir*	H	NH_2	$(HO)_2P(O)CH_2OCH_2$	*Cidofovir*
Valacyclovir	O	H	L-Val					
Ganciclovir	O	CH_2OH	H	*Famciclovir*	NH_2	H	$(AcOCH_2)_2CHCH_2$	
Valganciclovir	O	CH_2OH	L-Val					
Penciclovir	CH_2	CH_2OH	H					

Figure 1.

Keywords: *N*-Pivaloyloxymethyl sulfonamides; *N*-Mesyl-5-hydroxymethyl-1,3-oxazolidine; Acyclic azanucleosides; *Ganciclovir analogues*.
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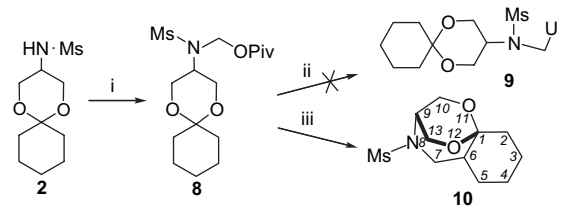
(pivaloyloxymethyl)ethyl]-methanesulfonamide or (ii) from 3-mesyl-4-(benzoyloxymethyl)-1,3-oxazolidine. These both substrates are easily accessible from 3-nitro-1,5-dioxaspiro[5.5]undecane **1**.[12] Antiviral activities of aza-analogues of *ganciclovir* are also reported.

2. Results and discussion

Nitrodioxane **1** was converted into the serinol derivative **4** in four steps (Scheme 1): (i) palladium catalyzed hydrogenation, (ii) reaction of the resulting amine with methanesulfonyl chloride (MsCl) in the presence of pyridine, (iii) acidic hydrolysis of **2**, (iv) O-pivaloylation of **3** with pivaloyl chloride in the presence of pyridine. The alkylation of **4** with chloromethyl pivaloate in the presence of sodium hydride in dry DMF gave *N*-(pivaloyloxymethyl)sulfonamide **5** required for the nucleoside coupling.

A one-pot base silylation/nucleoside coupling procedure was employed for the syntheses of protected azanucleosides **6C^{Bz}** and **6A^{Cbz}** (Scheme 1). Compound **5** was coupled with silylated N^4-Bz-cytosine (**C^{Bz}**) or N^6-Cbz-adenine (**A^{Cbz}**) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) or tin(IV) chloride, respectively.[13] Thus, these nucleobases were silylated with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in acetonitrile and subsequently **5** and a catalyst (Lewis acid) was added to afford **6C^{Bz}** or **6A^{Cbz}** in 72% or 44% yield, respectively. Heating of **6C^{Bz}** with ammonium hydroxide in methanol furnished deprotected azanucleoside **7C** in 83% yield. Deprotection of **6A^{Cbz}** was completed in two steps: (i) Cbz protecting group was removed by palladium catalyzed hydrogenolysis and (ii) hydroxy groups were deprotected by heating of the corresponding *O*-pivaloyl derivative with ammonium hydroxide to afford **7A** in 73% overall yield.

We also tried to obtain the uracil azanucleoside **9** from *N*-(pivaloyloxymethyl)-*N*-dioxanesulfonamide **8** (resulting from alkylation of **2** with chloromethyl pivaloate) (Scheme 2). However, attempts to couple **8** with silylated uracil (**U**) in the presence of TMSOTf failed. Instead of the expected derivative **9** the tricyclic derivative **10** was isolated in 39% yield from the complex reaction mixture.



Scheme 2. Reagents and conditions: (i) NaH, DMF, $ClCH_2OPiv$, rt, 72 h, 72%; (ii) uracil (**U**), BSA, TMSOTf, MeCN, rt, 24 h and (iii) Lewis acid (TMSOTf or $AlCl_3$ or $BF_3{\cdot}Et_2O$), MeCN, rt, 24 h, 39%.

A plausible pathway for formation of **10** from **8** in the presence of TMSOTf is shown in Scheme 3. According to the literature data,[14] we assume that **8** reacts with TMSOTf to give the intermediate enol ether **A**.

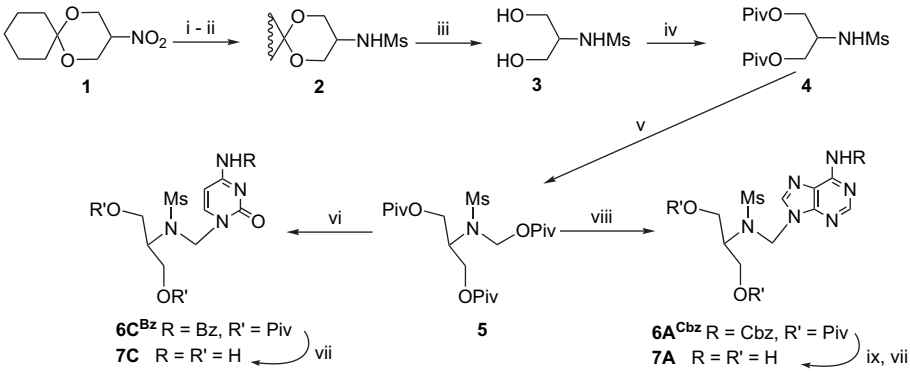
N-(Pivaloyloxymethyl)sulfonamide group is then converted into iminium cation **B** (Scheme 3), which undergoes intramolecular Mannich type reaction with the enol ether moiety. The process is completed with closure of the acetal ring to yield tricyclic derivative **10**.

The compound **10** was also obtained in the same yield in the presence of aluminum(III) chloride or boron trifluoride etherate.

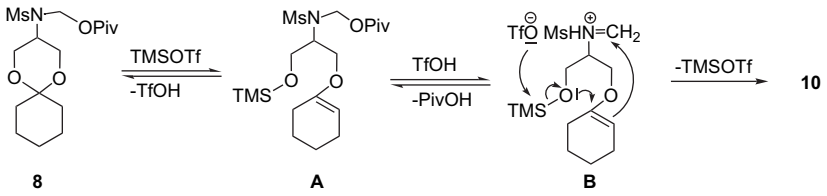
Unexpectedly, *N*-(pivaloyloxymethyl)-*N*-dioxanesulfonamide **8** underwent transformation into 3-mesyl-4-(hydroxymethyl)-1,3-oxazolidine **11** in 90% yield in the presence of a Brønsted acid [*p*-toluenesulfonic acid (PTSA) or Dowex-50(H^+)] in methanol (Scheme 4). Compound **11** was fully analyzed as *O*-benzoyl derivative **12** (Scheme 5).

Considering the literature data concerning the hydrolysis of *N*-(pivaloyloxymethyl)sulfonamides,[15] we assume that protonation of the carbonyl oxygen of the pivaloyl group with a Brønsted acid takes place. Then, loss of pivalic acid gives iminium cation **C**, which undergoes intramolecular rearrangement to give 1,3-oxazolidine intermediate **D**. The methanolysis of **D** gives **11**.

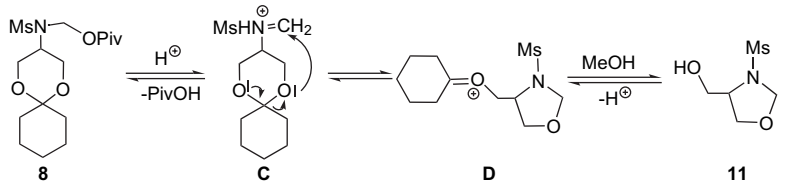
Some acyclic azanucleosides were prepared from 3-tosyloxazolidine-5-ones,[61] obtained from *N*-tosyl derivatives of



Scheme 1. Reagents and conditions: (i) H_2, 10% Pd/C, EtOH, rt, 60 bar, 24 h, quantitative; (ii) $MeSO_2Cl$ (MsCl), pyridine, CH_2Cl_2, rt, 67%; (iii) MeOH, Dowex-50 (H^+), rt, 48 h, 67%; (iv) PivCl, pyridine, rt, 24 h, 42%; (v) NaH, DMF, $ClCH_2OPiv$, rt, 72 h, 72%; (vi) N^4-Bz-cytosine (**C^{Bz}**), BSA, TMSOTf, MeCN rt, 24 h, 71%; (vii) NH_4OH_{concd}, MeOH, sealed tube, 70 °C, 1 d; (viii) N^6-Cbz-adenine (**A^{Cbz}**), BSA, $SnCl_4$, MeCN, 24 h, 44% and (ix) H_2 (balloon), 10% Pd/C, MeOH, rt, 1 d.



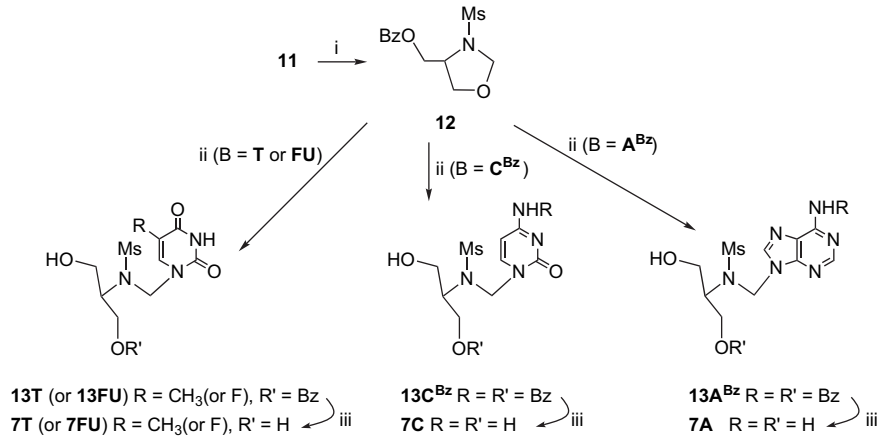
Scheme 3.



Scheme 4. Dowex-50(H^+) MeOH, rt, 1 d; 90% (crude).

amino acids. Consequently we envisaged that oxazolidine **11** could be used for the synthesis of aza-analogues of *ganciclovir* as well (Scheme 5, Table 1).

Crude **11** was treated with benzoyl chloride in the presence of pyridine in dry dichloromethane to afford *O*-benzoyl derivative **12** in 72% overall yield. The aforementioned one-pot base silylation/nucleoside coupling procedure was employed for the coupling of oxazolidine **12** with thymine (**B**=**T**), 5-fluorouracil (**B**=**FU**), N^4-Bz-cytosine (**B**=$\mathbf{C^{Bz}}$), N^6-Bz-adenine (**B**=$\mathbf{A^{Bz}}$) or N^2-acetyl-O^6-(diphenylcarbamoyl)guanine (**B**=$\mathbf{G^{PAC}}$). Accordingly, **12** and TMSOTf were added to the acetonitrile solution of the corresponding silylated nucleobase to yield compounds **13** (Table 1). Pyrimidine nucleosides **13** (**T**, **FU** or $\mathbf{C^{Bz}}$) were obtained in satisfactory yields, which were higher than that of the adenine derivative $\mathbf{13A^{Bz}}$. Attempts to obtain the guanine derivative using this procedure as well the original Robins' procedure[16] (nucleoside coupling was conducted in hot toluene in the presence of TMSOTf) were unsuccessful.[17] In the case of 5-fluorouracil and adenine derivatives (**13FU** and $\mathbf{13A^{Bz}}$, respectively) the yield was improved when TMSOTf was replaced by tin(IV) chloride (Table 1, entries 2–3 and 5–6). The *N*-1 or *N*-9 regioselectivity of the coupling was proved



Scheme 5. Reagents and conditions: (i) BzCl, pyridine, CH_2Cl_2, rt, 1 d, 72% (from **8**); (ii) **B**, BSA, catalyst (TMSOTf or $SnCl_4$), MeCN, rt, 2 d (for details see Table 1) and (iii) NH_4OH_{concd}, MeOH, rt, 1 d.

Table 1. Syntheses of aza-analogues of *Ganciclovir* **13** and **7**

Aza-analogues of *Ganciclovir* **13**					Aza-analogues *of Ganciclovir* **7**			
Entry	Base (**B**)	Catalyst	Nucleoside	Yield [%]	Entry	Base	Nucleoside	Yield [%]
1	Thymine (**T**)	TMSOTf	**13T**	67	7	Thymine (**T**)	**7T**	99
2	5-Fluorouracil (**FU**)	TMSOTf	**13FU**	44	8	5-Fluorouracil (**FU**)	**7FU**	80
3		$SnCl_4$		56				
4	N^4-Bz-cytosine ($\mathbf{C^{Bz}}$)	TMSOTf	$\mathbf{13C^{Bz}}$	66	9	Cytosine (**C**)	**7C**	74
5	N^6-Bz-Adenine ($\mathbf{A^{Bz}}$)	TMSOTf	$\mathbf{13A^{Bz}}$	14	10	Adenine (**A**)	**7A**	67
6		$SnCl_4$		26				

by ^{1}H–^{13}C HMBC correlations observed at thymine derivative **13T** or adenine derivative **13A^{Bz}**, respectively.

Treatment of compounds **13** with concd ammonium hydroxide in methanol at room temperature for 1 d afforded the azanucleosides **7** in high yields (Table 1, entries 7–10).

2.1. Antiviral activity

The antiviral activities of compounds **7** (**T**, **FU**, **C** or **A**), **13T** and **13FU** were evaluated in vitro against a variety of viruses. The following viruses and host cells were used for the evaluation:

(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.

Brivudin, (*S*)-9-(2,3-dihydroxypropyl)adenine ((*S*)-DHPA), *ribavirin*, *acyclovir* and *ganciclovir* were used as the reference compounds. Among them, only thymine derivative **13T** showed very low activity in test against respiratory syncytial virus in HeLa cell cultures (IC_{50}=49 μg/ml). In the same test *ribavirin* displayed IC_{50} of 9.6 μg/ml. The following minimum cytotoxic concentration values were estimated for tested azanucleosides:[18] (i) Vero cell cultures: 200 μM; (ii) E_6SM cell cultures: >200 μM and (iii) HeLa cell cultures: >200 μM.[19]

3. Conclusions

We have shown that the aza-analogues of *ganciclovir* can be readily obtained from *N*-[2-pivaloyloxy-1-(pivaloyloxymethyl)ethyl]methanesulfonamide **5** or 3-mesyl-4-(benzoyloxymethyl)-1,3-oxazolidine **11** by employing the one-pot base silylation/nucleoside coupling procedure. The oxazolidine **11** is useful for the synthesis of mono *O*-substituted aza-analogues of *ganciclovir*. Further studies on the improvement and extension of the methodologies described for the syntheses of various acyclic azanucleosides are in progress.

4. Experimental

4.1. General

High Resolution Mass Spectra (Electrospray Ionization, ESI) were performed on a Mariner™ spectrometer in positive ionization mode unless otherwise indicated. IR spectra were recorded on a Specord M80 (Carl-Zeiss Jena) spectrometer in KBr disc unless otherwise indicated; absorption maxima (ν_{max}) are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz and 50 MHz, respectively. ^{1}H and ^{13}C chemical shifts are reported in parts per million 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 'br s' (broad singlet). Coupling constants (*J*) are reported in Hertz. ^{13}C-NMR APT (Attached Proton Test) spectra were recorded on a Varian Gemini 200 spectrometer at 50 MHz; signals quoted as (–) indicate signals of carbon atoms from methyl (CH_3) or methylidene group (CH). 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, Merck). Solvents were purified by routine methods. The anhydrous $MgSO_4$ was employed as a drying agent. Solvents were distilled off under reduced pressure on a rotating evaporator.

4.1.1. 3-(Mesylamino)-1,5-dioxaspiro[5.5]undecane (2). 3-Nitro-1,5-dioxaspiro[5.5]undecane (**1**, 20.1 g, 0.1 mol)[12] in ethanol (100 cm^3) was hydrogenated under 60 bar pressure in the presence of 10% Pd/C (0.5 g) at room temperature for 24 h. The mixture was filtered through a Celite pad and the solvent was distilled off from the filtrate. The residue was dried in vacuum desiccator (over P_2O_5) for 24 h. The solution of the crude amine and pyridine (20.24 g, 0.2 mol, 27.9 cm^3) in DCM (160 cm^3) was cooled in ice water and the solution of methanesulfonyl chloride (17.2 g, 0.15 mol, 11.7 cm^3) in DCM (40 cm^3) was added dropwise. When the addition was completed, stirring was continued for 10 min. The mixture was washed subsequently with water (3×100 cm^3), diluted (5%) hydrochloric acid, water and dried. Solvent was distilled off and the residue was crystallized (ethyl acetate–hexane, 9/1, v/v) to yield **1** as white crystals (16.9 g, 67%), mp 101–103 °C. δ_H ($CDCl_3$) 1.52 (m, 8H), 1.84 (m, 2H), 3.01 (s, 3H), 3.41 (m, 1H), 3.75 (m, 2H), 4.14 (m, 2H), 5.30 (d, 1H, ^3J 9.0). δ_C ($CDCl_3$) 22.47, 22.56, 25.63, 28.15, 36.81, 42.51, 48.22, 63.57, 99.00. IR: 3324, 2944, 1312, 1164, 1136, 1104. HRMS (EI, 70 eV) *m/z* calcd for $C_{10}H_{19}NO_4S$ (M^+) 249.1032, found 249.1035.

4.1.2. *N*-[2-Pivaloyloxy-1-(pivaloyloxymethyl)ethyl]-methanesulfonamide (4). A mixture of **2** (1.0 g, 4 mmol) and Dowex-50(H^+) (1 g) in methanol (20 cm^3) was shaken at room temperature for 24 h. The ion exchange resin was filtered off and the solvent was distilled off. The residue was dried in vacuum desiccator (over P_2O_5) for 24 h, and then this was dissolved in dry pyridine (6 cm^3) and cooled in water bath. Pivaloyl chloride (1.16 g, 9.6 mmol, 1.2 cm^3) was added to this solution in one portion. The mixture was kept at room temperature for 24 h. The reaction was quenched by addition of water (16 cm^3) and DCM (4 cm^3). The organic phase was separated, washed with water, brine and dried. The solvent was distilled off and the residue was purified by flash chromatography (chloroform) to yield **4** (oil, 0.57 g, 42%). δ_H ($CDCl_3$) 1.27 (s, 18H), 3.02 (s, 3H), 3.98 (m, 1H), 4.17 (m, 4H), 4.81 (br s, 1H). δ_C ($CDCl_3$) 22.92, 39.06, 42.33, 52.11, 63.43 (×2), 97.14, 178.34. IR: 3288, 2976, 1728, 1320, 1156. HRMS *m/z* calcd for $C_{14}H_{27}NO_6NaS$ $(M+Na)^+$ 360.1451, found 360.1463.

4.1.3. *N*-(Pivaloyloxymethyl)-*N*-[2-pivaloyloxy-1-(pivaloyloxymethyl)ethyl]methanesulfonamide (5). A mixture of sodium hydride (63% suspension in mineral oil, 2.8 g,

70 mmol) and **4** (15.8 g, 35 mmol) in dry DMF (20 cm^3) was stirred at room temperature for 1 h. Then chloromethyl pivaloate (15.8 g, 105 mmol, 11.2 cm^3) was added in one portion. After 3 d of stirring at room temperature the mixture was poured into cold water (40 cm^3) followed by extraction with ethyl acetate (3×20 cm^3). The combined extracts were washed with water and dried. The low boiling solvents were distilled off under reduced pressure and residual DMF was removed in vacuum at 80 °C (0.05 mmHg). The residue was purified by flash chromatography (hexane–ethyl acetate, 3/1, v/v) to yield **5** as an oil (88%, 13.9 g). δ_H ($CDCl_3$) 1.21 (s, 27H), 3.09 (s, 3H), 4.27 (m, 5H), 5.53 (s, 2H). δ_C ($CDCl_3$) 27.15, 27.27, 38.95, 42.41, 54.26, 62.32, 70.58, 177.55, 178.04. IR: 2976, 1728, 1340, 1148. HRMS *m/z* calcd for $C_{20}H_{37}NO_8NaS$ $(M+Na)^+$ 474.2132, found 474.2126.

4.1.4. 4-(Benzoylamino)-1-{*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-1*H*-pyrimidin-2-one (6C^{Bz}). A mixture of N^4-benzoylcytosine (**B**=**C**^{Bz}, 430 mg, 2.0 mmol) and BSA (814 mg, 4.0 mmol, 1.0 cm^3) in dry acetonitrile (10 cm^3) was stirred at room temperature under argon for 1 h. Then a solution of **5** (363 mg, 1.0 mmol) in acetonitrile (1 cm^3) and TMSOTf (0.3 cm^3, 1.66 mmol) were added, successively. After 24 h the reaction mixture was quenched by the addition of $CHCl_3$ (50 cm^3) and a saturated solution of sodium bicarbonate (1 cm^3) and the resulting mixture was stirred for 1 h. Insoluble material was removed by filtration through a Celite pad. The organic layer was separated, washed with water, brine and dried. The solvent was distilled off and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 98/2, v/v) to give **6C**^{Bz} as amorphous foam, yield 71% (400 mg). δ_H ($CDCl_3$) 1.18 (s, 18H), 3.06 (s, 3H), 4.32 (m, 5H), 5.49 (s, 2H), 7.55 (m, 4H), 7.90 (m, 2H), 8.17 (d, ^3J 7.6, 1H), 8.78 (br s, 1H). δ_C ($CDCl_3$) 27.26, 38.89, 41.85, 56.67, 58.42, 62.04, 97.77, 127.74, 129.22, 132.94, 133.51, 148.41, 155.75, 163.00, 178.05. IR: 3308, 2976, 2932, 1732, 1696, 1676, 1556, 1484, 1340, 1312, 1276, 1252, 1148. HRMS *m/z* calcd for $C_{26}H_{37}N_4O_8S$ $(M+H)^+$ 565.2327, found 565.2346.

4.1.5. 4-Amino-1-{*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-1*H*-pyrimidin-2-one (7C). A mixture of **6C**^{Bz} (305 mg, 0.54 mmol), concd NH_4OH (1 cm^3) and MeOH (2 cm^3) was heated in a sealed tube at 70 °C for 24 h. The solvent was distilled off and the residue was purified by flash chromatography (acetone–methanol–NH_3 aq, 6/1/0.4, v/v/v) to give **7C** as white crystals, yield 74% (117 mg), mp 212–222 °C (dec). δ_H (DMSO-d_6) 3.06 (s, 3H), 3.44 (m, 4H), 3.79 (m, 1H), 4.90 (m, 1H), 5.19 (s, 2H), 5.76 (d, ^3J 7.4, 1H), 7.18 (s, 1H), 7.24 (s, 1H), 7.63 (d, ^3J 7.4 1H). δ_C (DMSO-d_6) 39.94, 55.49, 59.57, 62.04, 94.60, 143.98, 155.63, 165.81. IR: 3504, 3428, 3348, 3140, 1680, 1616, 1512, 1320, 1148. HRMS *m/z* calcd for $C_9H_{17}N_4O_5S$ $(M+H)^+$ 293.0914, found 293.0925.

4.1.6. 6-(Benzyloxycarbonylamino)-9-{*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-9*H*-purine (6A^{Cbz}). A mixture of the N^6-(benzyloxycarbonyl)adenine (**B**=**A**^{Cbz} 270 mg, 1.0 mmol) and BSA (814 mg, 4.0 mmol, 1.0 cm^3) in dry acetonitrile (10 cm^3) was stirred at room temperature under argon for 1 h, and then a solution of **5** (260 mg, 0.58 mmol) in acetonitrile (1 cm^3) and $SnCl_4$ (0.18 cm^3, 1.5 mmol) were added, successively. The resulted mixture was worked-up as described for **6C**^{Bz}. The residue was purified by flash chromatography ($CHCl_3$–acetone, 98/2, v/v) to give **6A**^{Cbz} as amorphous foam, yield 44% (158 mg). δ_H ($CDCl_3$) 1.08 (m, 18H), 2.96 (s, 3H), 4.27 (m, 5H), 5.28 (s, 2H), 5.75 (s, 2H), 7.45 (m, 5H), 8.43 (s, 1H), 8.74 (s, 1H), 9.26 (br s, 1H). δ_C ($CDCl_3$) 27.07, 38.72, 41.98, 52.05, 56.08, 61.93, 67.83, 121.36, 128.51, 128.62, 135.46, 143.54, 149.87, 151.02, 151.16, 153.17, 177.84. IR: 2976, 1732, 1616, 1588, 1472, 1340, 1284, 1212, 1148. HRMS *m/z* calcd for $C_{28}H_{38}N_6O_8NaS$ $(M+Na)^+$ 641.2364, found 641.2380.

4.1.7. 6-Amino-9-{*N*-[2-hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-9*H*-purine (7A). The mixture of **6A**^{Cbz} (141 mg, 22.8 mmol) and 10% Pd/C (20 mg) in MeOH (3 cm^3) was hydrogenated under atmospheric pressure (balloon) at room temperature for 2 d. The catalyst was filtered off through a short pad of Celite. Concd NH_4OH (1 cm^3) was added to the filtrate and the mixture was heated in a sealed tube at 70 °C for 24 h. The solvent was distilled off and the residue was purified by flash chromatography (chloroform–methanol, 9/1, v/v) to give **7A** as white crystals, yield 75% (54 mg), mp 240–242 °C. δ_H (DMSO-d_6) 3.10 (s, 3H), 3.47 (m, 4H), 3.82 (m, 1H), 5.00 (m, 2H), 5.65 (s, 2H), 7.36 (br s, 2H), 8.13 (s, 1H), 8.19 (s, 1H). δ_C (DMSO-d_6) 39.97, 51.47, 59.50, 61.93, 118.34, 140.29, 149.05, 152.67, 156.08. IR: 3324, 3160, 1664, 1600, 1332, 1152. HRMS *m/z* calcd for $C_{10}H_{17}N_6O_4S$ $(M+H)^+$ 317.1027, found 317.1042.

4.1.8. 3-[*N*-Mesyl-*N*-(pivaloyloxymethyl)amino]-1,5-dioxaspiro[5.5]undecane (8). A mixture of sodium hydride (63% suspension in mineral oil, 2.8 g, 70 mmol) and **2** (8.7 g, 35 mmol) in dry DMF (20 cm^3) was stirred at room temperature for 1 h. Then, chloromethyl pivaloate (15.8 g, 105 mmol, 11.2 cm^3) was added to the resulted suspension in one portion. After 3 d stirring at room temperature the reaction mixture was poured into ice water (40 cm^3). The mixture was extracted with ethyl acetate (3×20 cm^3) and the combined extracts were washed with water and dried. The solvents were distilled off and residual DMF was removed in vacuum (80 °C, 0.05 mmHg), successively. The residue was purified by flash chromatography (hexane–ethyl acetate, 3/1, v/v) to yield **8** as white crystals (9.2 g, 72%), mp 91–93 °C. δ_H ($CDCl_3$) 1.21 (s, 9H), 1.60 (m, 10H), 3.00 (s, 3H), 3.89 (m, 3H), 4.14 (m, 2H), 5.75 (s, 2H). δ_C ($CDCl_3$) 22.44, 22.65, 25.62, 27.22, 30.65, 34.08, 38.82, 42.27, 50.31, 62.33, 72.62, 98.77, 177.46. IR: 2936, 1712, 1332, 1164, 1156. HRMS *m/z* calcd for $C_{16}H_{29}NO_6NaS$ $(M+Na)^+$ 386.1608, found 386.1627.

4.1.9. 8-Mesyl-11,12-dioxa-8-aza-tricyclo[7.2.2.0^{1,6}]tridecane (10). A mixture of **8** (100 mg, 0.28 mmol) and a Lewis acid (TMSOTf, $AlCl_3$ or $BF_3 \cdot Et_2O$) (0.3 mmol) in acetonitrile (4 ml) was kept at room temperature for 24 h and then poured into a saturated solution of sodium bicarbonate. The product was extracted with ethyl acetate (2×2 cm^3). The combined extracts were washed with brine and dried. The solvent was distilled off and the residue was purified by flash chromatography (DCM) to give **10** as oil. δ_H ($CDCl_3$) 1.32–1.90 (m, 8H), 2.16 (m, 1H), 2.98 (s, 3H), 3.13 (dd, 1H, ^3J 9.5, ^2J 14.2), 3.75 (dd, 1H, ^3J 7.4,

^2J 14.2), 3.94 (dd, 1H, ^3J 2.0, ^3J 10.4), 4.01–4.09 (m, 2H), 4.19–4.24 (m, 2H). δ_C ($CDCl_3$, APT) 22.37, 24.61, 29.55, 38.97(–), 39.25, 46.50, 46.74(–), 51.67(–), 64.33, 65.02, 99.20. IR: 2932, 2860, 1320, 1256, 1196, 1144, 1112, 1052, 956. HRMS *m/z* calcd for $C_{11}H_{19}NO_4NaS$ $(M+Na)^+$ 284.0927, found 284.0929.

4.1.10. 3-Mesyl-4-(benzoyloxymethyl)-1,3-oxazolidine (12). A mixture of **8** (2.08 g, 5.5 mmol) and Dowex-50(H^+) (2.4 g) in methanol (50 cm^3) was shaken at room temperature for 24 h. The ion exchange resin was filtered off and the filtrate was concentrated to dryness. An analytical sample of **11** was purified by flash chromatography (methylene chloride). δ_H ($CDCl_3$) 2.69 (m, 1H), 2.89 (s, 3H), 3.68 (m, 3H), 3.88 (m, 1H), 4.26 (m, 1H), 4.52 (d, ^3J 7.2, 1H), 5.11 (d, ^3J 7.2, 1H). δ_C ($CDCl_3$) 35.90, 60.13, 63.10, 68.56, 81.13. IR: (neat) 3504, 3380, 3016, 2936, 2888, 1332, 1164, 1060.

The crude **11** was dissolved in dry DCM (4 cm^3). Dry pyridine (0.9 cm^3, 0.87 g, 11 mmol) and benzoyl chloride (0.7 cm^3, 0.84 g, 6 mmol) were added to that solution, subsequently. The mixture was left at room temperature for 24 h. Water (30 cm^3) was added and the mixture was stirred for 1 h. The organic layer was separated and the aqueous phase was extracted with DCM (2×10 cm^3). The organic phases were combined and washed with water and dried. The solvent was distilled off and the residue was crystallized from hexane–ethyl acetate mixture (1/1, v/v) to give **12** as white crystals, yield 72% (1.13 g), mp 102–103 °C. δ_H ($CDCl_3$) 2.91 (s, 3H), 3.78 (m, 1H), 4.29 (m, 2H), 4.44 (m, 2H), 4.62 (d, ^3J 7.1, 1H), 5.20 (d, ^3J 7.1, 1H), 7.45 (m, 2H), 7.59 (m, 1H), 8.04 (m, 2H). δ_C ($CDCl_3$) 37.04, 57.06, 64.70, 69.00, 80.97, 128.68, 129.52, 129.84, 133.55, 166.26. IR: (neat) 3012, 2932, 2892, 1708, 1456, 1340, 1284, 1160, 1128. HRMS *m/z* calcd for $C_{12}H_{15}NO_5NaS$ $(M+Na)^+$ 308.0563, found 308.0571.

4.2. Synthesis of azanucleosides 13

Azanucleosides **13** were obtained according to the procedure described for the syntheses of **6C^{Bz}** and **6A^{Cbz}** (for details see Table 1). For the syntheses of **13T** and **13C^{Bz}** a molar ratio of nucleobase (**B**)–BSA–Lewis acids–**12** was 2.0/4.0/1.66/1.0, respectively. In the case of the preparation of **13FU** and **13A^{Bz}** the above ratio was 2.0/4.0/3.0/1.0. The reaction mixtures were purified by flash chromatography to give the corresponding azanucleosides **13**; eluting solvents are given in parentheses below.

4.2.1. 1-{*N*-[2-Benzoyloxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (13T). Chromatographic purification (chloroform–methanol, 95/5, v/v) afforded **13T**, yield 67% (273 mg), mp 182–186 °C. δ_H (DMSO-d_6) 1.42 (s, 3H), 3.14 (s, 3H), 3.70 (m, 2H), 4.20 (m, 3H), 5.14 (d, ^2J 15.1, 1H), 5.27 (m, 1H), 5.41 (d, ^2J 15.1, 1H), 7.49 (m, 2H), 7.54 (s, 1H), 7.63 (m, 1H), 7.91 (m, 2H), 11.35 (br s, 1H). δ_C (DMSO-d_6) 11.80, 40.37, 54.82, 57.94, 58.43, 61.92, 109.77, 128.70, 129.14, 129.26, 133.39, 138.41, 151.14, 163.62, 165.26. IR: 3408, 3036, 1724, 1692, 1668, 1336, 1280, 1148. HRMS *m/z* calcd for $C_{17}H_{21}N_3O_7NaS$ $(M+Na)^+$ 434.0992, found 434.1000.

4.2.2. 1-{*N*-[2-Benzoyloxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (13FU). Chromatographic purification (chloroform–methanol, 93/7, v/v) afforded **13FU**, yield 44% (177 mg, TMSOTf) or 56% (230 mg, $SnCl_4$), mp 183–187 °C. δ_H (DMSO-d_6) 3.15 (s, 3H), 3.71 (m, 2H), 4.27 (m, 3H), 5.28 (m, 3H), 7.72 (m, 6H), 11.90 (br s, 1H). δ_C (DMSO-d_6) 40.20, 55.84, 58.19, 58.86, 62.06, 127.08 (d, $^2J_{C-F}$ 33.8), 128.72, 129.13, 133.48, 139.77 (d, $^1J_{C-F}$ 230.3), 149.84, 157.02 (d, $^2J_{C-F}$ 26.2), 165.35. IR: 3504, 3012, 2856, 1712, 1692, 1660, 1328, 1272, 1148, 1100. HRMS *m/z* calcd for $C_{16}H_{18}N_3O_7FNaS$ $(M+Na)^+$ 438.0742, found 438.0738.

4.2.3. 4-(Benzoylamino)-1-{*N*-[2-benzoyloxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-1*H*-pyrimidin-2-one (13C^{Bz}). Chromatographic purification (chloroform–methanol, 95/5, v/v) gave **13C^{Bz}**, yield 66% (324 mg), foam. δ_H (DMSO-d_6) 3.19 (m, 3H), 3.73 (m, 2H), 4.35 (m, 3H), 5.43 (m, 3H), 7.20–8.24 (m, 12H), 11.20 (br s, 1H). δ_C (DMSO-d_6) 40.17, 57.43, 58.62, 59.21, 62.64, 96.74, 128.47, 128.64, 129.19, 129.30, 129.38, 129.70, 132.78, 133.12, 133.35, 148.17, 155.33, 163.38, 167.23. IR: 3410, 3030, 1721, 1690, 1660, 1338, 1147. HRMS *m/z* calcd for $C_{23}H_{25}N_4O_7S$ $(M+H)^+$ 501.1438, found 501.1451.

4.2.4. 6-(Benzoylamino)-9-{*N*-[2-benzoyloxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-9*H*-purine (13A^{Bz}). Chromatographic purification (chloroform–acetone, 98/2, v/v) afforded **13A^{Bz}**, yield 14% (74 mg, TMSOTf) or 26% (138 mg, $SnCl_4$), foam. δ_H ($CDCl_3$) 2.74 (s, 3H), 4.06 (m, 2H), 4.39 (m, 1H), 4.55 (m, 2H), 4.94 (m, 1H), 5.88 (s, 2H), 7.52 (m, 6H), 7.98 (m, 4H), 8.36 (s, 1H), 8.77 (s, 1H), 9.17 (br s, 1H). δ_C ($CDCl_3$) 42.90, 53.96, 60.32, 61.30, 63.38, 123.33, 128.67, 129.34, 129.72, 129.94, 130.39, 133.81, 134.11, 134.24, 145.29, 150.82, 151.80, 153.54, 165.33, 166.86. IR: 3410, 1716, 1623, 1527, 1325, 1143. HRMS *m/z* calcd for $C_{24}H_{24}N_6O_6NaS$ $(M+Na)^+$ 547.1370, found 547.1383.

4.3. Deprotection of 13

Nucleosides **13** were treated with concd ammonium hydroxide in MeOH at room temperature for 24 h. The ratio of **13**–NH_4OH_{concd}–MeOH was 0.25 mmol/4 cm^3/4 cm^3, respectively. The reaction mixtures were evaporated to dryness under reduced pressure and the residues were purified by flash chromatography to give the corresponding azanucleosides: **7T**, **7FU**, **7C** or **7A** from **13T**, **13FU**, **13C^{Bz}** or **13A^{Bz}**, respectively (Table 1). The nucleosides **7C** and **7A** obtained from corresponding **13C^{Bz}** and **13A^{Bz}**, respectively, are identical with those obtained from **5**.

4.3.1. 1-{*N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-5-methyl-1*H*,3*H*-pyrimidin-2,4-dione (7T). Yield 99% (74 mg), (chloroform–methanol, 9/1, v/v, mp 160–187 °C). δ_H (DMSO-d_6) 1.77 (d, ^4J 1.2, 3H), 3.08 (s, 3H), 3.47 (m, 4H), 3.78 (m, 1H), 4.92 (m, 2H), 5.18 (s, 2H), 7.50 (q, ^4J 1.2, 2H). δ_C (DMSO-d_6) 12.30, 40.20, 54.87, 59.59, 62.04, 109.55, 138.69, 150.98, 163.96. IR: 3424, 3364, 1704, 1656, 1340, 1280, 1164, 1128. HRMS *m/z* calcd for $C_{10}H_{17}N_3O_6NaS$ $(M+Na)^+$ 330.0730, found 330.0744.

4.3.2. 1-{*N*-[2-Hydroxy-1-(hydroxymethyl)ethyl]mesylaminomethyl}-5-fluoro-1*H*,3*H*-pyrimidin-2,4-dione (7FU). Yield 80% (137 mg), chloroform–methanol–NH_3 aq, 7/3/0.5 and then 6/4/0.8, v/v/v, mp 172–190 °C (dec). δ_H (200 MHz, DMSO-d_6) 3.10 (s, 3H), 3.49 (m, 4H), 3.78 (m, 1H), 4.96 (m, 2H), 5.18 (s, 3H), 7.87 (d, $^3J_{F-H}$ 6.6, 1H). δ_C (50 MHz, DMSO-d_6) 39.67, 55.52, 59.48, 62.22, 127.17 (d, $^2J_{C-F}$ 33.8), 139.70 (d, $^1J_{C-F}$ 229.5), 149.61, 157.12 (d, $^2J_{C-F}$ 25.8). IR: 3512, 3436, 3064, 2836, 1700, 1348, 1316, 1260, 1144. HRMS *m/z* calcd for $C_9H_{14}N_3O_6FNaS$ $(M+Na)^+$ 334.0480, found 334.0496.

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17. In the light of successful synthesis of *N*-acetyl[9] and *N*-tosyl[10] acyclic aza-analogues of guanosine as well as adenosine (independently of kind of *N*-substituent), the fiasco of preparation of the *N*-mesyl analogue guanosine by various methods (Ref. 9 and this paper) is somewhat puzzling, indeed. Studies on solution of this problem are in progress.
18. Required to cause a microscopically detectable alteration of normal cell morphology.
19. The minimum cytotoxic concentrations of reference compounds were as follows: *brivudin* and *ribavirin* (Vero, E_6SM or HeLa cells, >400 μM); (*S*)-DHPA (Vero or HeLa cells, >400 μM); *acyclovir* (E_6SM cells, >400 μM); and *ganciclovir* (E_6SM cells, >100 μM).