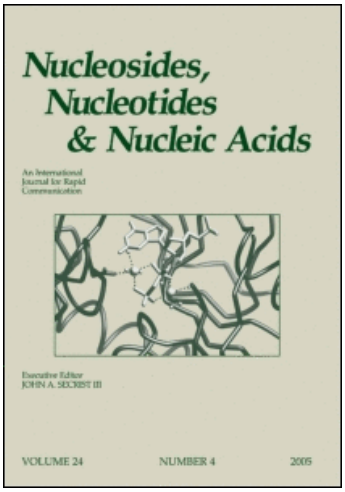

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis and Biological Activity of Some 5-Substituted-6-azauracil-N-1-Nucleosides of 2-Acetamido-2-Deoxy-D-glucose

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME 5-SUBSTITUTED-6-AZAURACIL-N-1-NUCLEOSIDES OF 2-ACETAMIDO-2-DEOXY-D-GLUCOSE

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Abstract. Glycosylation of the silylated 5-bromo- and 5-benzylmercapto-6-azauracil **1** and **2**, respectively, with the acylated sugar **3** afforded 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)-5-bromo-6-azauracil **4** and its 5-benzylmercapto analogue **6**. Deblocking of **4** and **6** gave the free nucleosides **5** and **7**, respectively. Alternatively, **6** was obtained from reaction of benzylmercaptan with **4** in pyridine. Reaction of **4** with morpholine, 2,4-dichlorobenzylamine and *N*-methylethanolamine gave the 5-alkylamino derivatives **8**, **10** and **11**, respectively. Deblocking of **8** gave the nucleoside **9**. All the newly synthesized compounds were characterized by their ^{1}H-NMR, U.V. and mass specta. Compounds **5**, **7**, **9**, **10** and **11** were tested for their activity against HIV type 1 and 2, but they did not show significant biological activity and not toxic at 100 mcg/mL. The antimutagenic activity of **5** and **7** is under investigation.

Several nucleosides with interchangable nitrogen and carbon atoms in their pyrimidine bases showe significant antimetabolic activities[1,2]. 6-Azauridine[3], the first reported example of such a nucleoside, exhibits remarkable activity against ascites lymphosarcoma[4] at 30 mg/kg i.p., while its 5'-monophosphate[3,5-10] is considered as a competitive inhibitor for ortidine-5'-monophosphate decarboxylase[10-12]. Ollapaly *et. al.*[13] have recently reported antiviral and *in vitro* antineoplastic activities of some keto unsaturated nucleosides of L-rhamnose carrying 6-azauracil and 5-fluorouracil.

In continuation of a program[14] to synthesize therapeutic active 6-azauracil nucleosides, we report herein the synthesis of new 5-substituted-6-azauracil nucleosides containing 2-acetamido-2-deoxy-D-glucose moieties as promising antiviral, antimutagenic, antineoplastic agents or enzyme inhibitors from the biochemical interest in D-glucosamine[15-17] and from the fact that 6-azauracil inhibit RNA formation[18] and possess carcinostatic properties[19,20].

SYNTHESIS

The 5-bromo compound **4** and its 5-benzylmercapto analogue **6** were obtained in 85% and 65% yield, respectively, by condensation of the silylated triazines[21] **1** or **2** with the acetylated sugar **3** according to the Hilbert-Johnson-Birkofer method[22] under trimethylsilyl triflate catalysis in boiling 1,2-dichloroethane. The products are highly water soluble and their isolation required evaporation of the solvent to dryness. Deblocking of **4**, **6** with methanolic-ammonia afforded **5** and **7** in 87% and 90% yield, respectively.

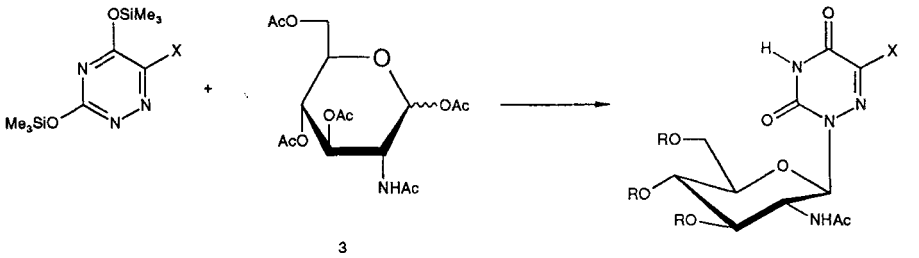
The syntheses of various 5-substituted 6-azauracil nucleosides from 5-bromo analogues have been reproted[23-27] showing the expected high reactivity and the facile displacement of the bromine residue by other biologically active groups. Thus, treatment of **4** with benzylmercaptan in boiling ethanol containing pyridine led to the formation of **6** in 58% yield. Similarly, treatment of **4** with morpholine in boiling ethanol/ pyridine afforded the 5-morpholino derivative in 70% yield. Transesterfication of **8** by Zemplen method[28] afforded **9** in 82% yield.

Displacement of bromine by amino groups required more drastic conditions. Thus, treatment of **4** with 2,4-dichlorobenzylamine or *N*-methylethanolamine in ethanol/pyridine at 100^{o} C under pressure afforded after chromatographic purification the 5-alkyamino derivatives **10** and **11** in 43% and 32% yield, respectively.

PHYSICAL PROPERTIES

The structures of the newly synthesized 6-azauracil-N-1-nucleosides were assigned on the basis of their UV (Table 1), ^{1}H-NMR and mass spectra (Table 2). The UV spectra showed close similarities to those of other 6-azauracil-N-1-nucleosides[19,25,27]. It has been observed from the spectra also that the monoanion formation is associated with a hypsochromic shift for the long wavelength band which is demonstrated partially in the MeOH spectra of the acylated and the free nucleosides.

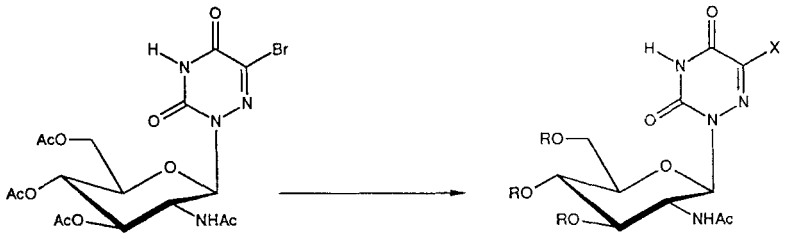
The ^{1}H-NMR spectra of compounds **4-11** showed doublets at δ ~ 5.0-5.9 for the anomeric proton. The large coupling constants (9.0-10.5 Hz) confirm the ß-configurations of the glycosidic linkages. The large values of $J_{2',3'}$, $J_{3',4'}$ and $J_{4',5'}$ (9.0-10.0 Hz) in **4-7** are



3

	X
1	Br
2	SCH_2Ph

	X	R
4	Br	Ac
5	Br	H
6	SCH_2Ph	Ac
7	SCH_2Ph	H



4

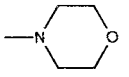
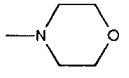
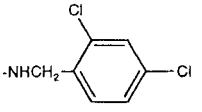
	X	R
8		Ac
9		H
10		H
11	$-N(CH_3)CH_2CH_2OH$	H

Table 1. UV and Mass Spectral Data of the 5-substituted 6-azauracil Nucleosides

Compound	pH Solvent	λ_{max} (nm)			log ε	Molecular ion	m/z
4	MeOH		274		4.01	0	478* (M^+-Ac)
5	MeOH		260		3.95	0	395# (MH^+)
	13		249		4.04	-	
6	MeOH	211	309	4.05	3.62	0	564* (M^+)
7	MeOH		310		3.78	0	438* (M^+)
	13	217	296	4.38	3.68	-	
8	MeOH		265		3.67	0	527* (M^+)
9	MeOH		268		3.64	0	402# (MH^+)
	13		250		3.76	-	
10	MeOH	[221]	[266]	[4.05]	[3.71]	0	512# (MNa^+)
	13	225	[260]	4.07	[4.32]	-	
11	MeOH		270		3.77	0	427# (MK^+)
	13		255		3.89	-	

[ ] = shoulder; 0 = neutral form; - = monoanion; (*)= molecular ion measured by EI-MS; (#): molecular ion measured by FAB-MS.

consistent with $^4C_1$ conformations of the sugar moiety. The signals for H-2' in these products showed splittings due to coupling to NH.

BIOLOGICAL EVALUATION

The prepared compounds **5**, **7**, **9**, **10** and **11** were tested for their *in vitro* inhibitory effects on the replication of anti-human immunodeficiency virus (anti HIV type 1 and 2). None of these compounds showed marked anti HIV-1 and 2 activity at a concentration less than 100 mcg/mL, and this concentration apparently did not show marked toxicity to the CEM cells.

EXPERIMENTAL

The melting points are uncorrected. The U.V. spectra were measured on a Perkin-Elmer spectrophotometer Lambda 5. The ^{1}H-NMR spectra were recorded at 250 MHz on a Bruker AC-250 spectrometer; TMS as an internal standard; δ -scale. T.l.c. was performed on silica gel 60 F_{254} sheet layer (Merck). Electron impact (EI) and FAB

[nitrobenzylalcohol (NBOH) as matrix] mass spectra have been performed by a MAT 312 mass spectrometer. Some molecular ions have been detected with K^+ and Na^+ ions.

1-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)-5-bromo-6-aza-uracil (4). A suspension of 5-bromo-6-azauracil (0.50 g, 2.61 mmol) in hexamethyldisilazane (20 mL) containing few crystals of $(NH_4)_2SO_4$ was boiled for 10 h. Evaporation of excess of hexamethyldisilazane under reduced pressure afforded **1**, which was dissolved in dry 1,2-dichloroethane (15 mL). A solution of **3** (1.02 g, 2.61 mmol) in dry 1,2-dichloroethane (15 mL) and trimethylsilyl triflate (0.48 mL, 2.61 mmol) were added. The reaction mixture was boiled under reflux for 1.5 h. After cooling to 23° C and concentration under reduced pressure to a volume of 5 mL the solid product (1.30 g) was filtered off. Recrystallization from EtOH/ Et_2O gave **4** (1.16 g, 85%) as colorless fine prisms; m.p. 235-237° C (dec); R_f= 0.28 [$CHCl_3$/ MeOH (4:1)].

Anal. Calc. for $C_{17}H_{21}BrN_4O_4$ (521.27): C, 38.17; H, 4.06; N, 10.76. Found: C, 37.94; H, 4.25; N, 10.42.

1-(2-Acetamido-2-deoxy-ß-D-glucopyranosyl)-5-bromo-6-azauracil (5). A solution of **4** (200 mg, 0.38 mmol) in 16% methanolic/ NH_3 (7 mL) was stirred at 23° C for 16 h. The solvent was evaporated to dryness under vaccum and the residue was partitioned between water and Et_2O. The aqueous layer was evaporated and the residue was co-evaporated with toluene/ EtOH (1:1) (3x5 mL). Recrystallization of the residue (160 mg) from isopropanol/ EtOH gave **5** (140 mg, 87%); m.p. 235-236° C; R_f= 0.34 [($CHCl_3$/ MeOH 3:2)].

Anal. Calc. for $C_{11}H_{15}BrN_4O_7$. 1½ H_2O (422.20): C, 31.29; H, 4.29; N, 13.27. Found: C, 31.26; H, 4.23; N, 12.84.

1-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-ß-D-glucopyranosyl)-5-benzyl-mercapto-6-azauracil (6). a. A mixture of 5-benzylmercapto-6-azauracil (0.41 g, 1.74 mmol) and hexamethyldisilazane (20 mL) was heated under reflux for 16 h with a catalytic amount of $(NH_4)_2SO_4$. Cooling and evaporation of excess of hexamethyldisilazane under vaccum with anhydrous condition gave **2**, which was dissolved in dry 1,2-dichloroethane (15 mL). After addition of a solution of **3** (0.66 g, 1.74 mmol) in dry 1,2-dichloroethane (15 mL) and trimethylsilyl triflate (0.31 mL, 1.74 mmol) the mixture was boiled under reflux for 15 h. Evaporation of the solvent under reduced pressure and co-evaporation of the residue with EtOH (3x10 mL) followed by $CHCl_3$ (3x10 mL) furnished a solid (0.70 g), which was recrystallized from

Table 2. ^{1}H-NMR Data of the 5-substituted 6-azauracil nucleosides in DMSO-d_6.

	NH	H-1' $J_{1',2'}$	H-2' $J_{2',3'}$	H-3' $J_{3',4'}$	H-4' $J_{4',5'}$	H-5' $J_{5',6'}$	H-6' $J_{5',6''}$	H-6'' $J_{6',6''}$
4	12.69s	5.91d (9.2)	4.21q (9.0)	5.32t (9.9)	4.89t (9.9)	3.96m (4.4)	4.19dd (7.8)	4.06dd (12.4)
5	12.68s	5.55d (9.4)	3.88q (9.3)	3.71m (9.3)	← 3.46m →		3.28dd (5.0)	3.16dd (10.0)
6	12.56bs	5.85d (10.5)	4.69q (9.7)	5.29t (10.2)	4.91t (9.2)	← 4.16-3.94m		→
7	12.36s	5.58d (9.2)	4.37q (9.2)	3.78m	←	3.44-3.14m		→
7*		5.56d (9.5)	4.40q (9.0)	3.51t (9.0)	3.47t (9.0)	3.46ddd (4.2)	3.31pt (6.5)	3.16pt (11.0)
8	13.50s	5.95d (9.5)	4.27q (9.5)	5.28pt (9.9)	4.86pt (9.7)	3.98m	4.26dd (8.0)	4.93m (12.6)
9	-	5.59d (9.3)	3.93q (9.0)	←3.57-3.39m →		← 3.36-3.08m		→
10	12.01s	5.63d (9.6)	3.96q (9.3)	3.66m	←	3.52-3.11m		→
11	12.20s	5.63d (9.8)	3.95q (9.8)	←3.70-3.55m →		←	3.50-3.30m	→

Multiplicities: s= singlet; d= doublet; dd= doublet of doublets; t= triplet; q= quartet; ddd= doublet of doublet of doublets; m= multiplet; pt= *pseudo*-triplet; bs= broad singlet. Coupling constants (Hz). (*)= in DMSO-d_6/ D_2O.

isopropanol/ EtOH to give **6** (0.60 g, 65%); m.p. 216-220° C (dec); R_f= 0.78 [($CHCl_3$/ MeOH 4:1)].

Anal. Calc. for $C_{24}H_{28}SN_4O_{10}$ (564.57): C, 51.06; H, 4.50; N, 9.92. Found: C, 50.82; H, 4.62; N, 9.83.

b. A solution of **4** (200 mg, 0.38 mmol) in dry EtOH (5 mL) containing dry pyridine (1 mL) was boiled, under N_2 with benzylmercaptan (2 mL) for 48 h. The solvent was evaporated under vaccum to dryness and the residue was co-evaporated with EtOH to give a solid (210 mg), which was recrystallized from isopropanol-EtOH to afford **6** (125 mg, 58%); m.p. 216-220° C (dec).

Table 2. ^{1}H-NMR Data of the 5-substituted 6-azauaracil nucleosides (continuation).

	OH-groups			NHAc	NHAc	Other Signals
	3',	4',	6',6"	$J_{2',NH}$		
4	-	-	-	7.93d (8.9)	1.67s	1.99, 1.97, 1.92 (OAc).
5	5.17d (5.2)	5.09d (5.7)	4.64m	7.79d (8.5)	1.72s	
6	-	-	-	7.96d (9.4)	1.72s	4.40d, 4.23d (CH_2) (J= 13.3 Hz); 1.99, 1.97, 1.93 (OAc); 7.49-7.26m (Ar).
7	5.18bs		4.65bs	7.84d (9.0)	1.76s	4.48d, 4.23d (CH_2) (J= 13.4 Hz).
8	-	-	-	7.92d (8.7)	1.79s	3.70bs, 3.02bs (CH_2); 2.00, 1.96, 1.90 (OAc).
9	3.71d (4.3)	3.57-3.39m		7.72d (9.0)	1.69s	3.71d, 3.00t (CH_2) (J= 4.9 Hz).
10	5.05-4.95m		4.91m	7.68d (9.2)	1.67s	3.74m (CH_2); 7.59d (NH-CH_2ph) (J= 7.7 Hz); 7.57-7.40m (Ar).
11	5.36d (5.0)	4.70m (9.0)		7.71d	1.69s	2.90m (OCH_2CH_2); 3.16t (NMe); 3.61t (OCH_2CH_2).

1-(2-acetamido-2-deoxy-ß-glucopyranosyl)-5-benzylmercapto-6-azauracil (7). Compound **6** (0.35 g, 0.65 mmol) was stirred at 23° C in 16% methanolic/ NH_3 (10 mL) for 18 h. Evaporation of the solvent under vaccum gave a solid (0.30 g), which was dissolved in water and extracted with Et_2O. The aqueous layer was evaporated to dryness under vaccum and the residue was lyophilized with EtOH (3x10 mL). Recrystallization from EtOH/ Et_2O gave **7** (0.26 g, 96%); m.p. 232-234° C (dec); R_f= 0.53 [($CHCl_3$/ MeOH 3:2)].

Anal. Calc. for $C_{18}H_{22}SN_4O_7$ (438.46): C, 49.31; H, 5.05; N, 12.78. Found: C, 48.92; H, 4.91; N, 12.62.

1-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranosyl)-5-morpholino-6-azauracil (8). A solution of **4** (190 mg, 0.36 mmol) in dry EtOH (10 mL)/ dry pyridine (2 mL) containing morpholine (2 mL) was boiled under reflux for 18 h. Evaporation of the solvent under vaccum and co-evaporation of the residue with EtOH/ toluene (1:1) (3x10 mL)) followed by Et_2O (2x10 mL) afforded an amorphous powder (190 mg). Crystallization from EtOH gave **8** (135 mg, 70%); starts to melt at 75° C and decomposed at 200° C; R_f= 0.43 [($CHCl_3$/ MeOH 9:1)].

Anal. Calc. for $C_{21}H_{29}N_5O_{11}$ (527.48): C, 47.82; H, 5.52; N, 13.27. Found: C, 47.61; H, 5.48; N, 13.39.

1-(2-Acetamido-2-deoxy-ß-D-glucopyranosyl)-5-morpholino-6-azauracil (9). A solution of **8** (150 mg, 0.28 mmol) in 16% methanolic/ NH_3 (7 mL) was stirred at 23° C for 16 h. The solvent was evaporated under vaccum and the residue was dissolved in water and extracted with Et_2O. The aqueous layer was evaporated under reduced pressure and the residue was co-evaporated with EtOH (3x5 mL) followed by Et_2O (3x5 mL) to afford a solid (110 mg), which was crystallized from EtOH/ Et_2O to give **9** (90 mg, 82%); starts to melt at 168° C and decomposed at 210° C; R_f= 0.53 [($CHCl_3$/ MeOH 3:2)].

Anal. Calc. for $C_{15}H_{23}N_5O_8 \cdot H_2O$ (419.39): C, 42.96; H, 5.77; N, 16.70. Found: C, 42.78; H, 5.63; N, 16.92.

1-(2-acetamido-2-deoxy-ß-D-glucopyranosyl)]-5-[(N-2-hydroxyethyl)amino]-6-azauracil (10). A solution of **4** (180 mg, 0.34 mmol) in dry EtOH (7 mL) containing dry pyridine (1 mL) and 2,4-dichlorobenzylamine (1.5 mL) was stirred under 20 bar at 100° C for 20 h. After cooling, the solvent was evaporated under vaccum and the residue was mixed with a small quantity of silica gel and co-evaporated with EtOH. Chromatography on a column of silica gel (10 g) with $CHCl_3$/ MeOH (2:1) as eluent removed an unidentified impurity (30 mg). Further elution with $CHCl_3$/MeOH (1:1) gave as colorless powder **10** (72 mg, 43%); m.p. 275-280° C (dec); R_f= 0.37 [($CHCl_3$/ MeOH 3:2)].

Anal. Calc. for $C_{18}H_{21}Cl_2N_5O_7$ (489.39): C, 44.17; H, 4.32; N, 14.31. Found: C, 44.01; H, 4.29; N, 14.18.

1-(2-Acetamido-2-deoxy-ß-D-glucopyranosyl)-5-[(N-2-hydroxyethyl)amino]-6-azauracil (11). A solution of **4** (200 mg, 0.38 mmol) in dry EtOH (7 mL) containing dry pyridine (1 mL) and *N*-methylethanolamine (48 mg, 0.76 mmol) was stirred at 100° C in an autoclave pressure vessel for 20 h. After cooling, the solvent was

evaporated under diminished pressure and the residue was partitioned between $CHCl_3$ (10 mL) and water (15 mL). The aqueous extract was evaporated under vaccum and the residue was co-evaporated with toluene/ EtOH (1:1) (3x10 mL). Chromatography on column of SiO_2 (10 g) using $CHCl_3$/ MeOH (1:1) as eluent gave **11** (48 mg, 32%) as a colorless powder; m.p.220-225^0 C; [R_f= 0.13 ($CHCl_3$/ MeOH 3:2)].

Anal. Calc. for $C_{14}H_{23}N_5O_8$. ½ H_2O (398.36): C, 42.21; H, 6.07; N, 17.58. Found: C, 42.56; H, 5.91; N, 17.81.

Mass

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