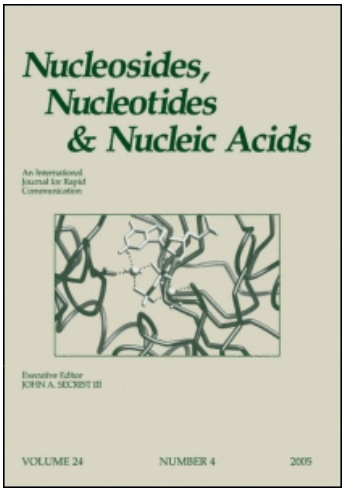

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Synthesis and Biological Activity of Some Unsaturated 6-Azauracil Acyclonucleosides

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME UNSATURATED 6-AZAURACIL ACYCLONUCLEOSIDES

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▫ *A useful route is described for obtaining Z and E unsaturated alkylating agents* ***3*** *and* ***4****. Coupling 6-azauracils* ***5*** *and* ***6*** *with unsaturated alkylating agent followed by the deprotection with* H^+ *resin gave acyclonucleosides* ***11–14*** *in good overall yields. Unsaturated acyclonucleosides phosphonates* ***19*** *and* ***20*** *were prepared using potassium carbonate as base and 4-bromobut-2-enyl diethyl phosphonate* ***16*** *as the alkylating agent. The introduction of a propargyl group at the N-3 position of acyclonucleosides* ***7****,* ***8****,* ***17****,* ***18****,* ***19****, and* ***20*** *was achieved using potassium carbonate in DMF.*

INTRODUCTION

Various nucleosides containing interchanged nitrogen and carbon atoms in their base moieties have shown considerable activity as antimetabolic agents.[1,2] For example, 5-azacytidine, 6-azauridine, and 6-azacytidine are the most important azanucleosides isolated or synthesized so far, from a clinical point of view.[3,4] 6-Azauridine[5] is the first reported example of such a nucleoside, exhibiting remarkable antitumor activity both experimentally and clinically. Several 6-azauracil nucleosides and acyclonucleosides analogues have been previously prepared.[7–9] More recently, attention has been centered on compounds derived

In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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from replacing the CH_2–O (ether) position in the respective acyclic derivatives with an olefinic bond HC=CH.[10,11]

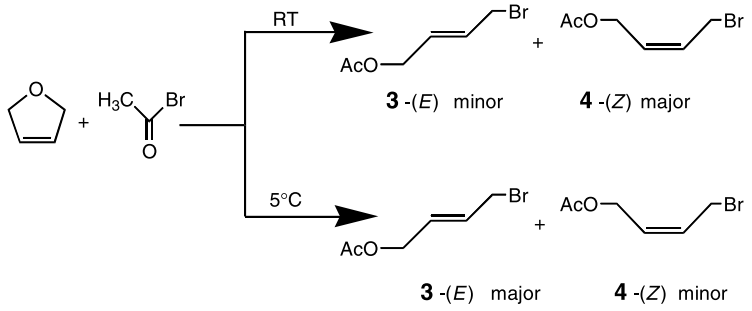
In order to search for more potent antiviral and/or antitumor agents, we undertook the development of highly efficient procedures for synthesizing unsaturated acyclic nucleosides of 6-azauracil and 5-bromo-6-azauracil with both Z and E configurations.

Our approach to the synthesis of 6-azauracil and 5-bromo-6-azauracil unsaturated acyclonucleosides containing the 4-hydroxybut-2-enyl group is based on the reaction of tetrahydrofuran with acetyl bromide which gives 4-bromobutyl acetate as a liquid in good yield.[12]

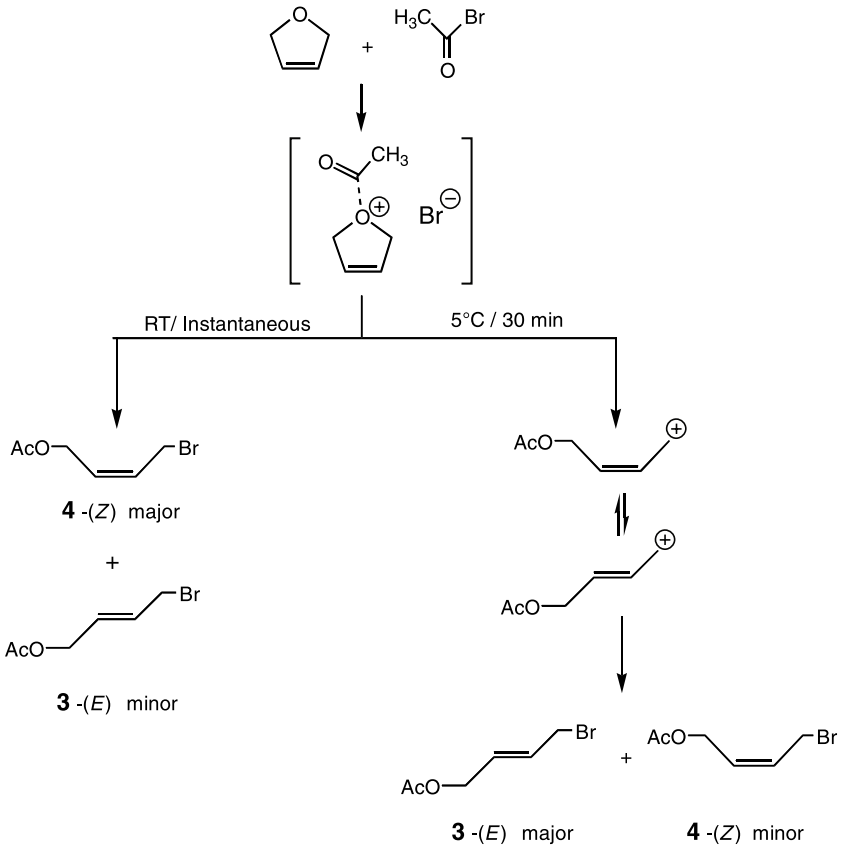
There are only a few examples of 2,5-dihydrofuran ring opening under acidic conditions.[13–17] Similar to earlier reports,[14,15] we found that treating commercially available 2,5-dihydrofuran with acetyl bromide (Scheme 1) at room temperature instantaneously gave a mixture of the *Z* and *E* isomers of 4-bromobut-2-enyl acetate in ratio 4/1. The *Z* isomer was also the major product in an earlier report of this reaction being conducted at 80°C.[15] The same result was obtained by Castillon et al.[16] using iodotrimethylsilane. On the other hand, Ohshita et al.[17] reported that refluxing 2,5-dihydrofuran with Et_2NSiMe_3/CH_3I gave exclusively the *E* isomer. Interestingly, when this reaction was performed at 5°C for 30 min (Scheme 1), the *E* isomer was obtained as the major product in 70% yield accompanied by the *Z* isomer in 30% yield. To explain this phenomenon we propose the following mechanism (Scheme 2).

This procedure constitutes an alternative to the synthesis of the separable (*Z*) **3** and (*E*) **4** alkenes. In every case, only the major product was isolated by fractional distillation. The percentage of each isomer was determined by ^{1}H-NMR spectroscopy.

The condensation between the nucleobases **5** and **6** with (*E*) or (*Z*)-1-acetoxy-4-bromobut-2-ene **3** and **4** (Scheme 3) was carried out using Na_2CO_3 in DMF at room temperature and gave the unsaturated acyclonucleosides **7**, **8**, **9**, and **10** (Table 1). After hydrolysis by H^+ resin in refluxing ethanol, the corresponding alcohols **11**, **12**, **13**, and **14** were obtained in good yields (Scheme 3). It is



SCHEME 1



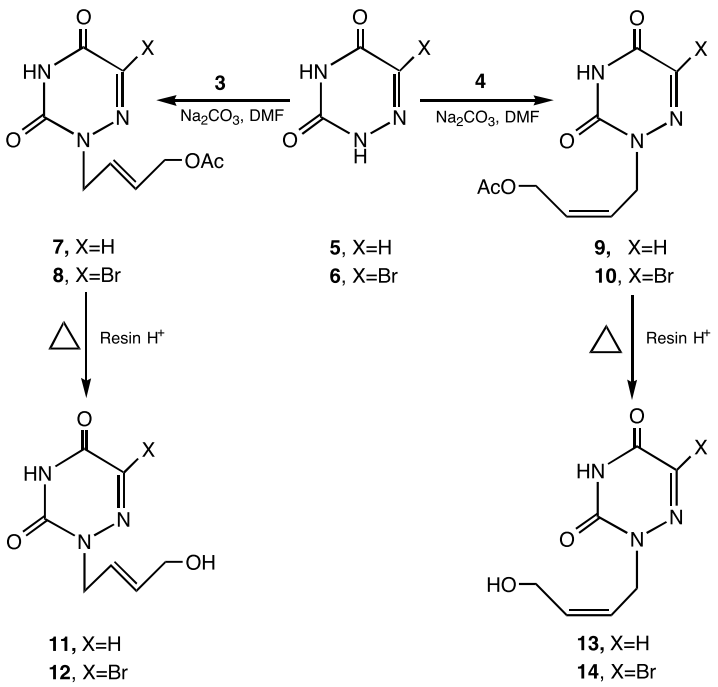
SCHEME 2

interesting to note that when a solution of methanol saturated with ammonia was used, depyrimidination occurred.

The ^{1}H NMR spectra of products **11–14** showed a multiplet at 5.35–5.73 ppm corresponding to vinylic protons H-2′ and H-3′. The site of alkylation of acyclonucleosides **11–14** was established as N-1 by the comparison of their UV spectra with their reported alkylated counterparts.[8]

We also attempted to prepare targets using alkylating agents with a phosphonate group in the 4 position, resulting in acyclonucleotide analogues **19** and **20**, since acyclonucleosides phosphonic acids display a wide variety of biological activities.[18] These targets were synthesized via two routes. Alkylation of the nucleobases **5** and **6** with (E)-1,4-dibromobutene **15** using Cs_2CO_3 and DMF at room temperature, gave (*E*)-bromo-alkenyl acyclonucleosides **17** and **18** in 30% yield. These compounds were then heated in refluxing triethyl phosphite to give unsaturated acyclonucleosides **19** and **20**, respectively, in 90% yields (Scheme 4).

For the second route, 4-bromobut-2-enyl diethyl phosphonate **16** was prepared via Michaelis-Arbuzov reaction, and this alkylating agent was condensed with the



SCHEME 3

nucleobases **5** and **6** using Na_2CO_3 and DMF at room temperature. Unsaturated acyclonucleoside phosphonates **19** and **20** were obtained in 61% and 75% yields, respectively, after chromatographic purification (Scheme 3). Unfortunately, we noticed that depyrimidination occurred when we tried to deprotect phosphonates **19** and **20** using trimethylsilylbromide.

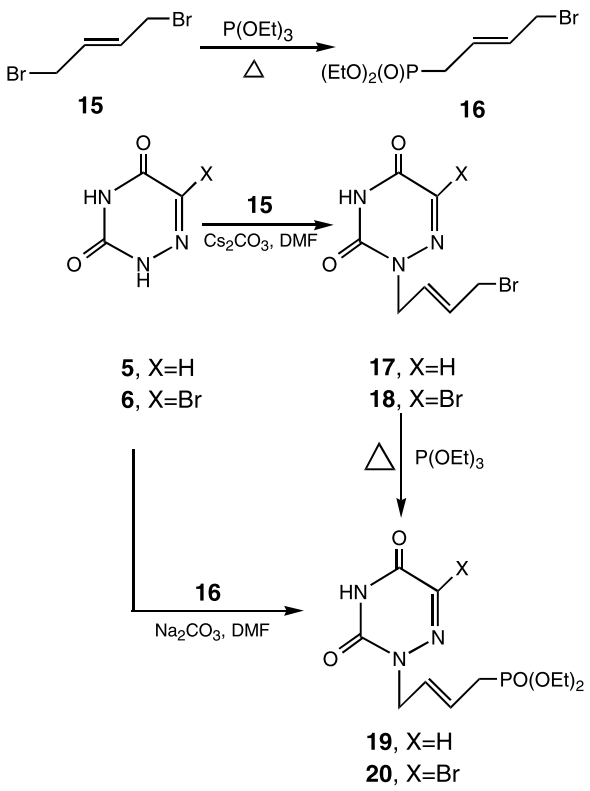
Recent reports from several laboratories have shown that modification at the N-3 position of pyrimidine nucleosides is applicable to the preparation of new nucleoside analogues displaying antiviral activity.[19–22] For this purpose the propargyl group was introduced at the N-3 position of unsaturated acyclonucleosides **7**,**8** and **17–20** (Scheme 4).

The alkylating agent, propargyl bromide, was condensed with the unsaturated acyclonucleosides **7**, **8**, and **17–20** using K_2CO_3 in DMF at room temperature.

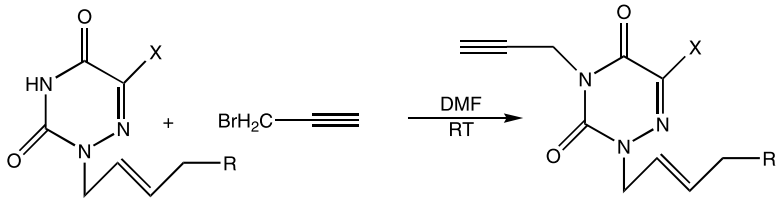
TABLE 1 Study of the N-1 Alkylation of 6-Azauracil **5**,**6**

Heterocycle	RX	t (h)	Yield (%)[a]
5	**3**-(*E*)	4	65
6		2	78
5	**4**-(*Z*)	2	50
6		1.5	63

[a]Yields were determined after purification by column chromatography.



SCHEME 4



7 X= H; R = OAc	**21**
8 X= Br; R = OAc	**22**
17 X= H; R = Br	**23**
18 X= Br; R = Br	**24**
19 X= H; R = $PO(OEt)_2$	**25**
20 X= Br; R = $PO(OEt)_2$	**26**

SCHEME *5*

TABLE 2 N-3 Alkylation Yields of **21–26**

Compounds	t (h)	Yield (%)[a]
21	4	48
22	3	93
23	1	85
24	1.5	50
25	2	82
26	2	85

[a]Yields were determined after purification by column chromatography.

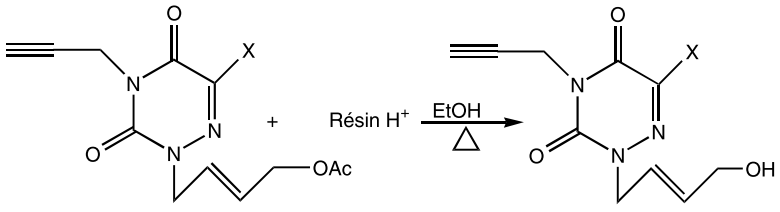
The bisalkylated unsaturated acyclonucleosides **21–26** were obtained in good yields (Table 2, Scheme 5).

Our attempts to alkylate isomers **9**-(*Z*) and **10**-(*Z*) at the N-3 position with propargyl bromide in alkaline solution led to the degradation of the starting material. For adducts **7** and **8** we found that H^+ resin in ethanol was the best medium to remove the acetyl group, and compounds **27** and **28** were obtained in good yields.

Antiviral Activity

Compounds **11–14**, **19** and **20** were evaluated for their inhibitory effect against the cytopathicity of HIV-1 (III_B) and HIV-2(ROD) in MT-4 cells.[23,24] No activity was observed for compounds **11–14** against the replication of these viruses at concentrations up to 100 μg/ml. On the other hand, compounds **19** and **20** showed activity at 7 μg/ml, but they were also very toxic at this concentration.

The unsaturated acyclonucleosides **21–28** were tested for their in vitro inhibitory effect on the replication of a number of DNA viruses (i.e., herpes simplex virus type 1 and 2, vaccinia virus) and RNA viruses (sindbis virus, coxsackie virus, polio virus) in three cell systems (Vero, E6SM and Hela). Compounds **21**, **22** and **25–28** showed interesting activity (data not shown) (Scheme 6).



21 **27**

22 **28**

SCHEME 6

EXPERIMENTAL

Melting point (mp) were determined on an electrothermal digital melting point apparatus and are uncorrected. Ultraviolet spectra (UV) were recorded with a CARY 219 spectrometer. The ^{1}H NMR spectra were recorded using a Bruker AC 250 MHz spectrometer. The chemical shifts were reported as δ (ppm) from TMS as the internal standard. Key: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Mass spectra (MS) were obtained with a JEOL JMS DX 300 instrument using fast atom bombardment (FAB^+). Thin layer chromatography (TLC) was performed on Kiesegel 60 F254 (Merck) plates, and short-wave ultraviolet light (254 nm) was used to detect the UV-absorbing spots. Column chromatography separations are performed on silica gel (0.063–0.2 mm, Merck). Elemental analyses were determined by French microanalytical central service (Vernaison).

(E)-4-Bromobut-2-en-1-yl acetate (3). Acetyl bromide (38.6 ml, 0.5 mol) was added dropwise under stirring to 2,5-dihydrofuran (39 ml, 0.5 mol) at temperature 0–5°C for 30 min, and the reaction mixture was distilled under vacuum to give 73.3 g (68%) of E isomer. ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.99–5.85 (m, 1H, CH = CH), 5.78 (m, 1H, CH = CH), 4.11 (d, 2H, J = 4.6 Hz, CH_2OAc), 3.91 (d, 2H, J = 6.7 Hz, CH_2Br), 2.09 (s, 3H, C*H*$_3$CO), MS (FAB^+, m/z): 194 $(M + H)^+$.

(Z)-4-Bromobut-2-en-1-yl acetate (4). Acetyl bromide (38.6 ml, 0.5 mol) was added dropwise under stirring to 2,5-dihydrofuran (39 ml, 0.5 mol) at room temperature, the exothermic reaction being controlled by the rate of acetyl bromide addition. The reaction mixture was stirred for 1 h and distilled under vacuum to give 53.3g (55%) of Z isomer. ^{1}H-NMR ($CDCl_3$) δ (ppm): 5.78–6.06 (m, 2H, CH = CH), 4.58 (d, 2H, J = 5.8 Hz, CH_2OAc), 3.95 (d, 2H, J = 6.7 Hz, CH_2Br), 2.09 (s, 3H, C*H*$_3$CO), MS (FAB^+, m/z): 194 $(M + H)^+$.

(*E*)-1-(4-Acetoxybut-2-enyl)-6-azauracil (7). A mixture of 6-azauracil (250 mg, 2.2 mmol), Na_2CO_3 (116 mg, 1.1 mmol) and (*E*)-4-bromobut-2-enyl acetate (500 mg, 2.6 mmol) in DMF (20 ml) was stirred for 2 h at room temperature. The solution was evaporated and the crude product was chromatographed on a silica gel column using EtOAc/hexane (80:20) as eluent to give the product **7** (247 mg, 65%): mp 82–84°C UV (methanol) λ_{max} = 258.6 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.63 (s, 1H, NH), 7.50 (s, 1H, H_5), 5.67 (m, 1H, $H_{2'}$), 5.55 (m, 1H, $H_{3'}$), 4.71 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 5.8 Hz), 4.40 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.9 Hz), 2.02 (s, 3H, C*H*$_3$CO), MS (FAB^+, m/z) : 226 $(M + H)^+$. Anal. calcd. for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 47.96; H, 4.99; N, 18.58.

(*E*)-1-(4-Acetoxy but-2-enyl)-5-bromo-6-azauracil (8). The procedure for compound **7** was used to synthesize compound **8** (217 mg, 55%): mp 106–108°C UV (methanol) λ_{max} = 275.5 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 5.67 (m, 1H, $H_{2'}$), 5.55 (m, 1H, $H_{3'}$), 4.71 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 5.9 Hz),

4.40 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.7 Hz), 2.02 (s, 3H, C*H*$_3$CO), MS (FAB$^+$, m/z): 305 (M + H)$^+$. Anal. calcd. for $C_9H_{10}BrN_3O_4$: C, 35.55; H, 3.31; N, 13.82. Found: C, 35.53; H, 3.34; N, 13.79.

(*Z*)-1-(4-Acetoxybut-2-enyl)-6-azauracil (9). A mixture of 6-azauracil (250 mg, 2.2 mmol), Na_2CO_3 (116 mg, 1.1 mmol) and (*Z*)-4-bromobut-2-enyl acetate (500 mg, 2.6 mmol) in DMF (20 ml) was stirred for 1 h at room temperature. The solution was evaporated and the crude product was chromatographed on a silica gel column with EtOAc/hexane (80:20) to give the product **9** (247 mg, 50%): mp 110–112°C UV (methanol) λ_{max} = 258.6 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.63 (s, 1H, NH), 7.56 (s, 1H, H_5), 5.75 (m, 2H, $H_{2'}$ and $H_{3'}$), 4.50 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.1 Hz), 4.38 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.3 Hz), 2.02 (s, 3H, C*H*$_3$CO); MS (FAB$^+$, m/z): 226 (M + H)$^+$. Anal. calcd. for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.08; H, 5.00; N, 18.54.

(*Z*)-1-(4-Acetoxybut-2-enyl)-5-bromo-6-azauracil (10). The procedure for compound **9** was used to synthesize compound **10** (217 mg, 55%): UV (methanol) λ_{max} = 275.3 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 5.75 (m, 2H, $H_{2'}$ and $H_{3'}$), 4.50 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 5.9 Hz), 4.38 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.7 Hz), 2.02 (s, 3H, C*H*$_3$CO), MS (FAB$^+$, m/z): 305 (M + H)$^+$. Anal. calcd. for $C_9H_{10}Br N_3O_4$: C, 35.55; H, 3.31; N, 13.82. Found: C, 35.50; H, 3.38; N, 13.75.

Deprotection Method

To 1 mol of acetylated acyclonucleoside was added 45 ml of H^+ resin. The solution was stirred for 12 h at reflux of ethanol. Thin-layer chromatography indicated that complete deprotection of the acyclonucleoside had occurred. Volatile materials were evaporated and the residue was purified by chromatography.

(*E*)-1-(4-Hydroxybut-2-enyl)-6-azauracil (11). UV (methanol) λ_{max} = 257.6 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.63 (s, 1H, NH); 7.56 (s, 1H, H_5), 5.73 (m, 1H, $H_{2'}$), 5.35 (m, 1H, $H_{3'}$), 4.70 (s, 1H, OH), 4.43 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.6 Hz); 4.25 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.9 Hz), MS (FAB$^+$, m/z): 184 (M + H)$^+$. Anal. calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.80; H, 5.06; N, 22.84.

(*E*)-1-(4-Hydroxybut-2-enyl)-5-bromo-6-azauracil (12). UV (methanol) λ_{max} = 273.8 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 5.73 (m, 1H, $H_{2'}$), 5.35 (m, 1H, $H_{3'}$), 4.75 (s, 1H, OH), 4.43 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.6 Hz), 4.25 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.9 Hz); MS (FAB$^+$, m/z): 263 (M + H)$^+$. Anal. calcd. for $C_7H_8Br N_3O_3$: C, 32.08; H, 3.08; N, 16.03. Found: C, 32.06; H, 3.12; N, 16.00.

(*Z*)-1-(4-Hydroxybut-2-enyl)-6-azauracil (13). UV (methanol) λ_{max} = 257.4 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.57 (s, 1H, NH), 7.56 (s, 1H, H_5), 5.75 (m, 1H, $H_{2'}$), 5.65 (m, 1H, $H_{3'}$), 4.76 (s, 1H, OH), 4.38 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.7 Hz),

3.92 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 5.9 Hz), MS (FAB^+, m/z): 184 $(M + H)^+$. Anal. calcd. for $C_7H_9N_3O_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.83; H, 5.02; N, 22.85.

(*Z*)-1-(4-Hydroxybut-2-enyl)-5-bromo-6-azauracil (14). UV (methanol) λ_{max} = 273.2 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 5.75 (m, 1H, $H_{2'}$), 5.65 (m, 1H, $H_{3'}$), 4.75 (s, 1H, OH), 4.38 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.8 Hz), 4.25 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.0 Hz), MS (FAB^+, m/z): 263 $(M + H)^+$. Anal. calcd. for $C_7H_8Br\ N_3O_3$: C, 32.08; H, 3.08; N, 16.03. Found: C, 32.18; H, 3.15; N, 15.97.

(*E*)-1-(4-Bromobut-2-enyl)-6-azauracil (17). A mixture of 6-azauracil (250 mg, 2.2 mmol), Cs_2CO_3 (460 mg, 3.3 mmol) and (E) 1,4-dibromobut-2-ene (570 mg, 2.6 mmol) in DMF (20 ml) was stirred for 0.5 h at room temperature. The solution was evaporated and the crude product was chromatographed on a silica gel column with EtOAc/hexane (70:30) to give the product **17** (244 mg, 45%): mp 98–100°C UV (methanol) λ_{max} = 257.8 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.63 (s, 1H, NH); 7.40 (s, 1H, H_5), 6.05 (m, 1H, $H_{2'}$), 5.85 (m, 1H, $H_{3'}$), 4.55 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.4 Hz), 3.90 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 7.3 Hz), MS (FAB^+, m/z): 247$(M + H)^+$. Anal. calcd. for $C_7H_8Br\ N_3O_2$: C, 34.17; H, 3.28; N, 17.08. Found: C, 34.20; H, 3.36; N, 16.96.

(*E*)-1-(4-Bromobut-2-enyl)-5-bromo-6-azauracil (18). The procedure for compound **17** was used to synthesize compound **18** (211 mg, 50%): mp 128–130°C UV (methanol) λ_{max} = 274.4 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 6.05 (m, 1H, $H_{2'}$), 5.85 (m, 1H, $H_{3'}$), 4.55 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.3 Hz), 3.90 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 7.2 Hz); MS (FAB^+, m/z): 326 $(M + H)^+$. Anal. calcd. for $C_7H_7Br_2N_3O_2$: C, 25.87; H, 2.17; N, 12.93. Found: C, 25.99; H, 2.21; N, 12.76.

Diethyl (*E*)-4-(6-azauracil-1-yl)but-2-enephosphonate (19). Method-1: Compound **17** (300 mg, 1.2 mmol) was heated in refluxing triethyl phosphite (10 ml) for 6 h. The excess of triethyl phosphite was evaporated and the residue was chromatographed on a silica gel column with EtOAc/hexane (25:75) to give the product **19** (362 mg, 93%): mp 98–100°C UV (methanol) λ_{max} = 258.8 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.63 (s, 1H, NH), 7.35 (s, 1H, H_5), 5.72 (m, 2H, $H_{2'}$ and $H_{3'}$), 4.45 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 9.2 Hz), 4.10 (qd, 4H, CH_2, J_{CH2CH3} = 7.0 Hz, J_{PCH2} = 8.0 Hz), 2.60 (dd, 2H, $H_{4'}$, $J_{4'3'}$ = 6.5 Hz, $J_{H4'P}$ = 21.7 Hz), 1.28 (t, 6H, $2CH_3$, J_{CH3CH2} = 7.0 Hz), MS (FAB^+, m/z): 304 $(M + H)^+$. Anal. calcd. for $C_{11}H_{18}N_3O_5P$: C, 43.57; H, 5.98; N, 13.96. Found: C, 43.51; H, 5.96; N, 13.65.

Method-2: A mixture of 6-azauracil (250 mg, 2.2 mmol), Na_2CO_3 (233 mg, 2.2 mmol), and diethyl (E)-4-bromobut-2-enephosphonate (704 mg, 2.6 mmol) in DMF (20 ml) was stirred for 3 h at room temperature. After work-up and purification the product **19** was obtained (433 mg, 65%).

Diethyl (*E*)-4-(5-bromo-6-azauracil-1-yl)but-2-enephosphonate (20). Using method 1, compound **20** was obtained with 90% yield. UV (methanol) λ_{max} = 277.6 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.85 (s, 1H, NH), 5.72 (m, 2H, $H_{2'}$ and $H_{3'}$), 4.45 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 9.0 Hz), 4.10 (qd, 4H, CH_2, J_{CH2CH3} = 6.9 Hz, J_{PCH2} = 8.0 Hz), 2.60 (dd, 2H, $H_{4'}$, $J_{4'3'}$ = 6.5 Hz, $J_{H4'P}$ = 21.7 Hz), 1.28 (t, 6H, $2CH_3$, J_{CH3CH2} = 7.0 Hz), MS (FAB$^+$, m/z): 383 $(M + H)^+$. Anal. calcd. for $C_{11}H_{17}BrN_3O_5P$: C, 34.57; H, 4.48; N, 11.00. Found: C, 34.45; H, 4.49; N, 10.96.

PREPARATION OF N-1,N-3-BISALKYL ACYCLONUCLEOSIDES

A mixture of 1.45 mmol of acyclonucleosides (**7**, **8**, **17–20**), K_2CO_3 (1.45 mmol) and 4.35 mmol of propargyl bromide in DMF (20 ml) was stirred for 1 to 4 h at room temperature. The solution was evaporated and the crude product was purified by silica gel column chromatography.

1-[(E)-(4-Acetoxybut-2-enyl)]3-propargyl-6-azauracil (21). UV methanol λ_{max} = 264.8 nm; NMR ^{1}H ($CDCl_3$), δ (ppm): 7.41(s, 1H, H_5); 5.85 and 5.67 (2m, 2H, $H_{2'}$ and $H_{3'}$); 4.84 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 7.12 Hz); 4.75(d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.41 Hz); 4.62 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.99 Hz); 2.41 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.41 Hz); 2.10 (s, 3H, CH_3). MS (FAB$^+$, m/z): 264 $(M + H)^+$. Anal. calcd. for $C_{12}H_{13}N_3O_4$ C, 54.75; H, 4.98; N, 15.96. Found: C, 54.82; H, 5.06; N, 15.86.

1-[(*E*)-(4-Acetoxybut-2-enyl)]3-propargyl-5-bromo-6-azauracil (22). UV methanol λ_{max} = 279.3 nm; NMR ^{1}H ($CDCl_3$) δ (ppm): 5.80 and 5.62 (2m, 2H, $H_{2'}$ and $H_{3'}$); 4.82 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.88 Hz); 4.75(d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.49 Hz); 4.61(d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.99 Hz); 2.41 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.49 Hz); 2.05 (s, 3H, CH_3). MS (FAB$^+$, m/z): 343 $(M + H)^+$. Anal. calcd. for $C_{12}H_{12}Br\ N_3O_4$: C, 42.13 ; H, 3.35; N, 12.28. Found: C, 42.07; H, 3.41; N, 12.19.

1-[(*E*)-(4-Bromobut-2-enyl)]-3-propargyl-6-azauracil (23). UV (methanol) λ_{max} = 265.6 nm; ^{1}H-NMR ($CDCl_3$) δ (ppm): 7.38 (s, 1H, H_5), 5.96 (m, 1H, $H_{2'}$), 5.73 (m, 1H, $H_{3'}$), 4.68 (d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.4 Hz), 4.46 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 7.0 Hz), 3.83 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 7.1 Hz), 2.34 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.4 Hz). MS (FAB$^+$, m/z): 285 $(M + H)^+$. Anal. calcd. for $C_{10}H_{10}Br\ N_3O_2$: C, 42.28; H, 3.55; N, 14.79. Found: C, 42.32; H, 3.61; N, 14.70.

1-[(E)-(4-Bromobut-2-enyl)]5-bromo-3-propargyl-6-azauracil (24). UV methanol λ_{max} = 279.8 nm; NMR ^{1}H ($CDCl_3$), δ (ppm): 5.94 and 5.71 (2m, 2H, $H_{2'}$ and $H_{3'}$); 4.68(d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.45 Hz); 4.44 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 7.18 Hz); 3.81 (d, 2H, $H_{4'}$, $J_{4'3'}$ = 6.96 Hz); 2.34 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.45 Hz). MS (FAB$^+$, m/z): 365 $(M + H)^+$. Anal. calcd. for $C_{10}H_9Br_2\ N_3O_2$: C, 33.09; H, 2.50; N, 11.58. Found: C, 33,18; H, 2.62; N, 11.47.

Diethyl (*E*)-4-(3-propargyl-6-azauracil-1-yl)but-2-enephosphonate (25). UV (methanol) λ_{max} = 266.8 nm; ^{1}H-NMR (DMSO-d6), δ (ppm): 7.67 (s, 1H, H_5), 5.64 (2m, 2H, $H_{2'}$ and $H_{3'}$), 4.72 (d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.4 Hz), 4.36 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.9 Hz), 3.97 (q, 4H, CH_2-OP, J_{CH2CH3} = 7.0 Hz), 3.41 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.4 Hz), 2.63 (dd, 2H, $H_{4'}$, $J_{4'3'}$ = 6.3 Hz, $J_{4'P}$ = 21.8 Hz), 1.20 (t, 6H, CH_3-C*H*$_2$-OP, J_{CH2CH3} = 7.0 Hz). MS (FAB$^+$, m/z): 285 (M + H)$^+$. Anal. calcd. for $C_{14}H_{20}N_3O_5P$: C, 49.27; H, 5.91; N, 12.31. Found: C, 49.18; H, 6.00; N, 12.22.

Diethyl (*E*)-4-(5-bromo-3-propargyl-6-azauracil-1-yl)but-2-enephosphonate (26). UV methanol λ_{max} = 280.4 nm; NMR ^{1}H (DMSO-d6), δ (ppm): 5.62 (2m, 2H, $H_{2'}$, and $H_{3'}$); 4.72 (d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.45 Hz); 4.34 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 5.97 Hz); 3.95(q, 4H, CH_2-OP, J_{CH2CH3} = 7.14 Hz); 3.40 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.45 Hz); 2.63 (dd, 2H, $H_{4'}$, $J_{4'3'}$ = 6.38 Hz, $J_{4'P}$ = 21.90 Hz); 1.20 (t, 6H, CH_3-CH_2-OP, J_{CH2CH3} = 7.14 Hz). MS (FAB$^+$, m/z): 421 (M + H)$^+$. Anal. calcd. for $C_{14}H_{19}BrN_3O_5P$: C, 40.02; H, 4.56; N, 10.00. Found: C, 40.00; H, 4.55; N, 9.94.

Deprotection of Compounds 21 and 22

To 100 mg of acetylated acyclonucleosides **21** or **22** was added 10 ml of ethanol and 1 g of H^+ Resin. The solution was stirred for 12 h in refluxing ethanol. Thin-layer chromatography indicated that complete deprotection of acyclonucleoside had occurred. Volatile materials were evaporated and the residue was purified by chromatography.

1-[(E)-(4-Hydroxybut-2-enyl)]-3-propargyl-6-azauracil (27). UV methanol λ_{max} = 265.8 nm; NMR ^{1}H (DMSO-d6) δ (ppm): 7.65 (s, 1H, H_5); 5.69 and 5.36 (2m, 2H, $H_{2'}$ and $H_{3'}$); 4.78 (d, 1H, OH, J = 5.29 Hz); 4.75 (d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.28 Hz); 4.44 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.37 Hz); 4.15 (t, 2H, $H_{4'}$, J = 5.85 Hz); 3.42 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.28 Hz). MS (FAB$^+$, m/z): 222 (M + H)$^+$. Anal. calcd. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 5.01; N, 19.00. Found: C, 54.20; H, 5.09; N, 18.88.

1-[(E)-(4-Hydroxybut-2-enyl)]-5-bromo-3-propargyl-6-azauracil (28). UV methanol λ_{max} = 279.4 nm; NMR ^{1}H (DMSO-d6) δ (ppm): 5.62 and 5.30 (2m, 2H, $H_{2'}$ and $H_{3'}$); 4.72 (d, 1H, OH, J = 5.32 Hz); 4.69 (d, 2H, $H_{1''}$, $J_{1''3''}$ = 2.36 Hz); 4.43 (d, 2H, $H_{1'}$, $J_{1'2'}$ = 6.37 Hz); 4.09 (t, 2H, $H_{4'}$, J = 5.50 Hz); 3.45 (t, 1H, $H_{3''}$, $J_{3''1''}$ = 2.36 Hz). MS (FAB$^+$, m/z): 301 (M + H)$^+$. Anal. calcd. for $C_{10}H_{10}BrN_3O_3$: C, 40.02; H, 3.36; N, 14.00. Found: C, 39.99; H, 3.37; N, 13.98.

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