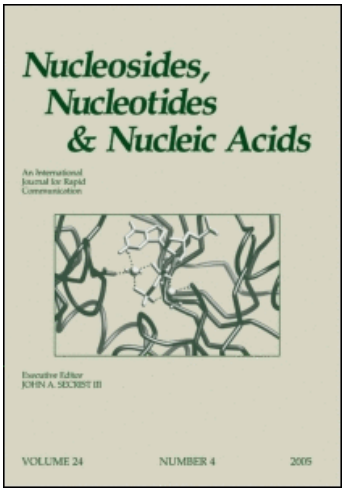

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Synthesis of Racemic 5-Substituted 1-(2,3-Dihydroxypropyl)-6-azauracils and Their Isosteric Isomers

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SYNTHESIS OF RACEMIC 5-SUBSTITUTED 1-(2,3-DIHYDROXYPROPYL)-6-AZAURACILS AND THEIR ISOSTERIC ISOMERS

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Abstract

Acyclic nucleoside analogues of antiviral DHPA and HPMPA have been prepared. Coupling of silylated 6-azauracils with benzyl glycidyl ether and stannic chloride followed by the deprotection with boron trichloride gave 1-(2,3-dihydroxypropyl)-6-azauracils (**3**) in good overall yields. Reaction of silylated 6-azauracil and epichlorohydrin with or without catalytic stannic chloride afforded 1-(2-chloro-3-hydroxypropyl)-6-azauracil (**4a**) and 1-(3-chloro-2-hydroxypropyl)-6-azauracil (**6a**) respectively. Coupling of silylated 6-azaisocytosine under the same reaction conditions provided 1-(2,3-dihydroxypropyl)-6-azaisocytosine (**9**) and 1-(2-chloro-3-hydroxypropyl)-6-azaisocytosine (**10**) respectively. None of the compounds exhibited significant antiviral activity against herpes simplex viruses.

Introduction

The potent antiviral activity of acyclic nucleosides, 9-(*S*)-(2,3-dihydroxypropyl)adenine (DHPA)[1-4] and 9-(*S*)-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (HPMPA)[5-7] against the virus multiplication prompted the synthetic and biological studies of their analogues. DHPA acts as a potent inhibitor of S-adenosy-L-homocysteine hydrolase

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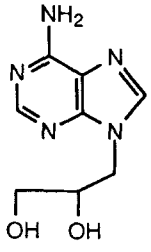
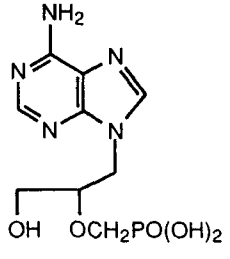
(SAH-hydrolase) leading to the accumulation of SAH in the cells which affects the methylation, cellular processes important for viral multiplication. The antiviral spectrum of HPMPA is totally different from that of DHPA and other adenosine analogues. In fact, HPMPA possesses potent and selective activity against a broad spectrum of DNA viruses which are normally insensitive to currently available antiviral drugs.

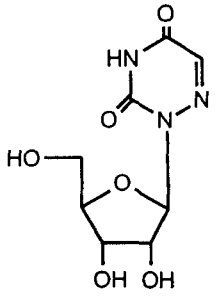
6-Azauracil, a bioisosteric isomer of uracil, has been found to display a range of biological effects which include antiviral,[8-9] antitumor,[10-11] and antifungal[12]activities. Its ribonucleoside, 6-azauridine, exerts carcinostatic activity against a number of experimental tumors.[13] The mechanism of action has been ascribed to the *in vivo* formation of 6-azauridine-5'-phosphate, a competitive inhibitor of orotidine-5'-phosphate (OMP) decarboxylase with an inhibition constant K_i of 0.03 mM.[14-15]



DHPA



HPMPA

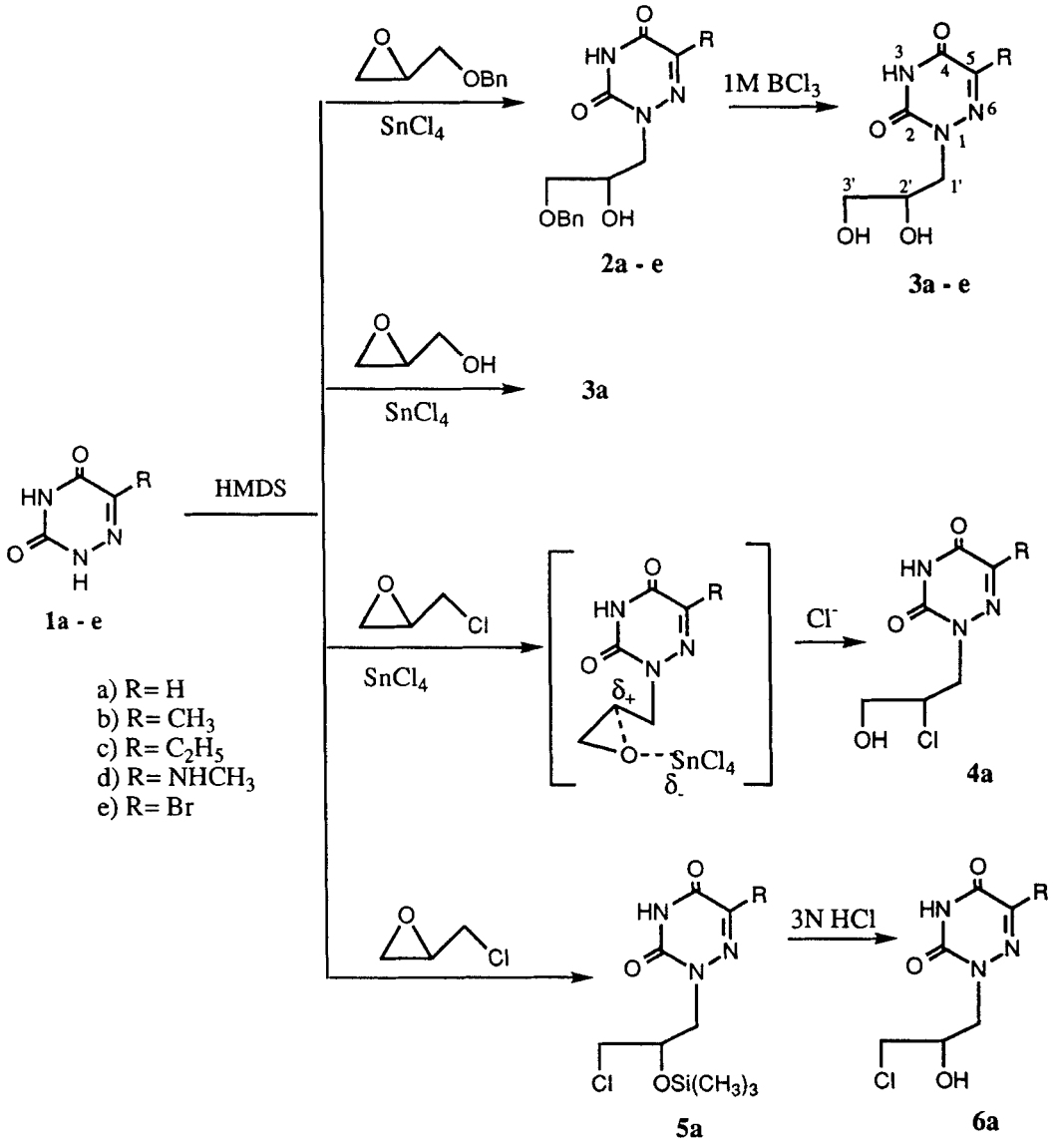


6-Azauridine

In view of the unique biological properties and chemotherapeutic activities exhibited by DHPA, HPMPA, and 6-azauridine, we initiated the present study to explore the new acyclic nucleosides in which the acyclic residue of DHPA is attached to 6-azauracil and 6-azaisocytosine in an attempt to search for more potent antiviral and/or antitumor agents. The 5-position of 6-azauracil was substituted with halogen and alkyl groups whereas the acyclo sugar moiety was modified at 2'- or 3'-position by substitution with a chlorine atom. Other 6-azauracil acyclonucleosides have been previously described.[16-20]

Results and Discussion

The preparation of DHPA analogues (**3**) is illustrated in Scheme 1. 6-Azauracil (**1a**)[21-24] was silylated with hexamethyldisilazane (HMDS) and then reacted with benzyl glycidyl ether and a catalyst of stannic chloride ($SnCl_4$) to furnish 1-(3-benzyloxy-2-hydroxy-propyl)-6-azauracil (**2a**) in 76% yield. Debenzylation of **2a** with either H_2/palladiun hydroxide or boron trichloride afforded 1-(2,3-dihydroxypropyl)-6-azauracil (**3a**) in a high yield. When 1-(3-benzyloxy-2-hydroxypropyl)-5-bromo-6-azauracil (**2e**) was subjected to catalytic hydrogenation, the bromo group was replaced and **3a** was produced in 92% yield.



Scheme 1

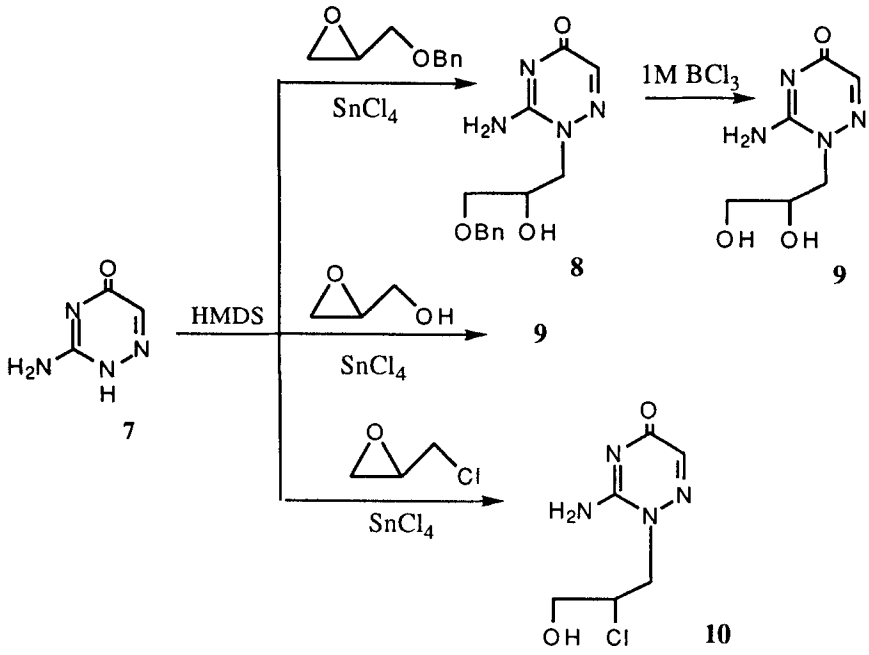
To obtain 5-bromo-1-(2,3-dihydroxypropyl)-6-azauracil (**3e**), the starting material **2e** should be deprotected by using boron trichloride. Compound **3a** can also be prepared directly from the silylated intermediate of **1a** and glycidol in 71% yield. Alkylation of silylated **1a** with one molar equivalent of epichlorohydrin and a catalytic amount of $SnCl_4$ in a non-polar solvent (dry toluene or dry dichloromethane) gave an epoxide intermediate which underwent an S_N1-like ring opening to afford the desired 1-(2-chloro-3-hydroxypropyl)-6-azauracil (**4a**). When the same reaction was run without adding the catalyst ($SnCl_4$), **4a** was not obtained. The ^1H NMR spectrum of the sole product isolated in this reaction showed two singlets at δ 0.10 and 7.34 ppm, two doublets at δ 3.50 and 4.10 ppm, and one multiplet at δ 4.11 ppm corresponding to $OSi(CH_3)_3$, H-5, CH_2Cl, NCH_2, and OCH respectively.The ^{13}C NMR spectrum supported the ^1H NMR spectrum in confirming the presence of two methylene carbons resonances appeared at δ 43.73 and 46.91 ppm, one tertiary carbon resonance at δ 69.34 ppm and the trimethylsilyl carbons resonance at δ -0.01 ppm. The mass spectrum which shows the fragments of *m/z* 241 (M^+-HCl) and 228 (M^+-CH_2Cl) indicated the presence of terminal chloromethyl group. The elemental analysis was in accord with the molecular formula $C_9H_{16}ClN_3O_3Si$, which taken together with spectral evidence suggested a structure of 1-(3-chloro-2-trimethylsilyloxypropyl)-6-azauracil (**5a**). The site of glycosylation of **1** was established as N_1 but not N_3 by the comparison of UV spectra with their reported ribosylated counterparts.[25] Hydrolysis of **5a** with aqueous HCl provided 1-(3-chloro-2-hydroxypropyl)-6-azauracil (**6a**) in 83% yield. When the silylated intermediate of 6-azaisocytosine (**7**) was reacted with benzyl glycidyl ether in the presence of a catalytic $SnCl_4$, 1-(3-benzyloxy-2-hydroxypropyl)-6-azaisocytosine (**8**) was obtained (Scheme 2). Debenzylation of **8** with BCl_3 afforded 1-(2,3-dihydroxypropyl)-6-azaisocytosine (**9**). Compound **9** can also be prepared directly from **7** and glycidol. Reaction of the silylated **7** with epichlorohydrin and $SnCl_4$ gave the desired 1-(2-chloro-3-hydroxypropyl)-6-azaisocytosine (**10**).

Antiviral Studies

Antiviral and cytotoxicity assays of the new acyclic nucleosides (**3a-e**, **4a**, **6a**, **9** and **10**) against HSV-1 and HSV-2 in Human Foreskin Fibroblast (HFF) cell were performed by the cytopathic effect (CPE) inhibition assay. None of the compounds were active against HSV-1 and HSV-2 or exhibited toxic effects in uninfected HFF cell when tested up to 100 mM.

Experimental

Melting points were determined on a YANACO micromelting point apparatus and are uncorrected. The ultraviolet absorption spectra were obtained on a Beckman UV-Visible



Scheme 2

spectrophotometer. Infrared spectra were recorded on a Hitachi 260-30 spectrophotometer. Nuclear magnetic resonance (^1H and ^{13}C)spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane as an internal standard. Thin-layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the UV absorbing sports. Elemental analyses were carried out on a Heraeus CHN-O-Rapid elemental analyzer.

1-(3-Benzyloxy-2-hydroxypropyl)-6-azauracil **(2a).**

6-Azauracil (**1a**, 1.13 g, 10 mmol), HMDS (25 ml), and ammonium sulfate (0.1g) were heated under reflux with the exclusion of moisture until a clear solution was obtained. The excess HMDS was removed under vacuo and the residual oil dissolved in dry CH_2Cl_2 (20 ml). To this solution was added benzyl glycidyl ether (1.64 g, 10 mmol) in dry CH_2Cl_2 (15 ml) and the resulting reaction mixture was allowed to stir at 0 °C. $SnCl_4$ (0.76 ml, 6.5 mmol) was added slowly and the reaction was continued for 2 h (monitored by TLC). Methanol (20 ml) was added to quench the reaction and the organic solvent was evaporated to give an residual oil which was purified by silica gel chromatography using a mixed solvent of $CHCl_3$: MeOH (8:1) to afford **2a** (2.1 g; 76%). ^1H-NMR ($CDCl_3$) δ

3.53 (br s, 1H, OH), 3.57 (m, 2H, NCH_2), 4.00 (m, 1H, CH), 4.10 (d, 2H, OCH_2), 4.57 (s, 2H, Ar-CH_2), 7.34 (s, 5H, Ar), 7.38 (s, 1H, H-5); ^{13}C-NMR (DMSO-d_6) δ 53.75 (C-1'), 68.72 (C-2'), 71.38 (C-3'), 73.56 (Ar-C), 135.33 (C-5), 148.70 (C-2), 156.20 (C-4).

The same procedure was used to convert each of the compounds **1b-e** to the respective **2b-e**.

1-(3-Benzyloxy-2-hydroxypropyl)-6-azathymine (**2b**).

Yield 56%; ^{1}H-NMR ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.69 (m, 2H, NCH_2), 3.88 (m, 3H, OCH_2 & CH), 4.51 (s, 2H, Ar-CH_2), 4.92 (br s, 1H, OH), 7.27 (s, 5H, Ar).

1-(3-Benzyloxy-2-hydroxypropyl)-5-ethyl-6-azauracil (**2c**).

Yield 64%; ^{1}H-NMR ($CDCl_3$) δ 1.13 (t, 3H, CH_3), 2.56 (q, 2H, CH_2), 3.56 (m, 2H, NCH_2), 3.93 (m, 1H, CH), 4.20 (d, 2H, OCH_2), 4.56 (s, 2H, Ar-CH_2), 4.92 (br s, 1H, OH), 7.31 (s, 5H, Ar), 10.70 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 10.43 (CH_3), 23.33 (CH_2), 53.80 (C-1'), 69.38 (C-2'), 72.33 (C-3'), 74.05 (Ar-C), 149.13 (C-5), 151.09 (C-2), 158.01 (C-4).

1-(3-Benzyloxy-2-hydroxypropyl)-5-methylamino-6-azauracil (**2d**).

Yield 72%; ^{1}H-NMR (DMSO-d_6) δ 2.78 (d, 3H, CH_3), 3.56 (m, 2H, NCH_2), 4.01 (m, 3H, CH & OCH_2), 4.56 (s, 2H, Ar-CH_2), 5.54 (q, 1H, $NHCH_3$), 7.32 (s, 5H, Ar), 10.97 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 28.07 (CH_3), 53.02 (C-1'), 69.33 (C-2'), 72.24 (C-3'), 73.79 (Ar-C), 144.16 (C-5), 149.44 (C-2), 154.70 (C-4).

1-(3-Benzyloxy-2-hydroxypropyl)-5-bromo-6-azauracil (**2e**).

Yield 80%; ^{1}H-NMR ($CDCl_3$) δ 3.51 (m, 2H, NCH_2), 4.04 (m, 3H, CH & OCH_2), 4.50 (s, 2H, Ar-CH_2), 7.25 (s, 5H, Ar), 10.41 (br s, 1H, NH); ^{13}C-NMR ($CDCl_3$) δ 54.40 (C-1'), 69.11 (C-2'), 71.77 (C-3'), 74.03 (Ar-C), 129.68 (C-5), 149.76 (C-2), 153.78 (C-4).

1-(2,3-Dihydroxypropyl)-6-azauracil (**3a**).

Method A: To an ice-salt cooled solution of **2a** (1.39 g, 5 mmol) in dry dichloromethane (30 ml) was added boron trichloride in dichloromethane (5 ml, 1 M solution). The mixture was stirred at the same temperature (-8°C) for 30 min (monitored by TLC to ensure the reaction was completed). A solution (40 ml) of MeOH and CH_2Cl_2 (1:1) was then added and the resulting mixture was allowed to warm to room temperature. The solvent was evaporated under reduced pressure to give a solid residue which was crystallized from a mixed solvent of CH_2Cl_2 and MeOH to give **3a** (0.59 g, 85% yield). mp 110 - 111 °C; UV: λmax (log ε) 282 (3.70) (0.1N HCl), 282 (3.75) (H_2O), 281 (3.59) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6) δ 3.36 (m, 2H, NCH_2), 3.83 (m, 3H, OCH_2 & OCH), 4.64 (t, 1H, 3'-OH), 4.87 (br s, 1H, 2'-OH), 7.45 (s, 1H, H-5), 12.10 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 53.63 (C-1'), 63.63 (C-3'), 68.79 (C-2'), 134.94 (C-5),

148.48 (C-2), 157.15 (C-4); MS: *m/z* 188 $(M+1)^+$; Anal. Calcd for $C_6H_9N_3O_4$: C, 38.51; H, 4.85; N, 22.45. Found: C, 38.23; H, 4.94; N, 22.40.

Method B: 6-azauracil (**1a**, 1.13 g, 10 mmol) was suspended in hexamethyldisilazane (HMDS; 25 ml) and then a catalytic amount of ammonium sulfate (0.1 g) was added. The mixture was heated under reflux with the exclusion of moisture until a clear solution was obtained (ca. 4 h). Excess HMDS was removed under reduced pressure to give silylated intermediate as an oil which was dissolved in dry CH_2Cl_2 (20 ml) and cooled to 0 °C. To this stirred solution was added glycidol (0.74 g, 10 mmol) and $SnCl_4$ (0.76 ml, 6.5 mmol). The reaction mixture was stirred at 0 °C for 2 h (monitored by TLC). The solvent was evaporated to afford the crude product which was crystallized from a mixed solvent of CH_2Cl_2 and MeOH to give **3a** (1.33g, 71% yield).

Method C: Compound **2a** or **2e** (3 mmol), palladium hydroxide on carbon (600 mg), cyclohexene (5 ml) and absolute ethanol (35 ml) were refluxed for 4 h (monitored by TLC). The resulting solution was filtered and the filtrate evaporated to give the crude product which was crystallized as above to give **3a** (88% yield from **2a** and 92% yield from **2e**).

Method B was adopted for the preparation of **3b-e**.

1-(2,3-Dihydroxypropyl)-6-azathymine (**3b**).

Yield 65%; mp 156 - 157 °C (CH_2Cl_2 and MeOH); UV: λmax (log ε) 283 (3.77) (0.1N HCl), 283 (3.64) (H_2O), 280 (3.63) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6) δ 2.06 (s, 3H, CH_3), 3.34 (m, 2H, NCH_2), 3.73 (m, 3H, OCH_2 & OCH), 4.48 (t, 1H, 3'-OH), 4.70 (br s, 1H, 2'-OH), 11.94 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 15.97 (CH_3), 53.72 (C-1'), 63.72 (C-3'), 68.96 (C-2'), 142.78 (C-5), 149.41 (C-2), 157.64 (C-4); MS: *m/z* 201 (M^+); Anal. Calcd for $C_7H_{11}N_3O_4$: C, 41.79; H, 5.51; N, 20.89. Found: C, 41.59; H, 5.55; N, 20.73.

1-(2,3-Dihydroxypropyl)-5-ethyl-6-azauracil (**3c**).

Yield 60%; mp 148 - 149 °C (CH_2Cl_2 and MeOH); ^{1}H-NMR (DMSO-d_6) δ 1.08 (t, 3H, CH3), 2.47 (q, 2H, CH_2), 3.35 (m, 2H, NCH_2), 3.81 (m, 3H, OCH_2 & OCH), 4.64 (t, 1H, 3'-OH), 4.83 (d, 1H, 2'-OH), 11.92 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 10.49 (CH_3), 22.78 (CH_2), 53.52 (C-1'), 64.23 (C-3'), 69.44 (C-2'), 147.17 (C-5), 150.20 (C-2), 158.19 (C-4); MS: *m/z* 184 (M^+-CH_2OH); Anal. Calcd for $C_8H_{13}N_3O_4$: C, 44.65; H, 6.09; N, 19.53. Found: C, 44.54; H, 6.10; N, 19.42.

1-(2,3-Dihydroxypropyl)-5-methylamino-6-azauracil (**3d**).

Yield 69%; mp 157 - 159 °C (CH_2Cl_2 and MeOH); UV: λmax (log ε) 311 (3.64) (0.1N HCl), 312 (3.78) (H_2O), 300 (3.60) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6) δ 2.10 (d, 3H, CH_3), 3.38 (m, 2H, NCH_2), 3.69 (m, 2H, OCH_2), 3.88 (m, 1H, CH), 4.62 (t, 1H, 3'-OH), 4.80 (d, 1H, 2'-OH), 6.72 (q, 1H, $NHCH_3$), 11.87 (br s, 1H, NH); ^{13}C-NMR

(DMSO-d_6) δ 27.57 (CH_3), 52.18 (C-1'), 63.93 (C-3'), 68.90 (C-2'), 143.65 (C-5), 148.37 (C-2), 154.59 (C-4); MS: *m/z* 216 (M^+); Anal. Calcd for $C_7H_{12}N_4O_4$: C, 38.89; H, 5.59; N, 25.92. Found: C, 38.73; H, 5.62; N, 25.73.

5-Bromo-1-(2,3-dihydroxypropyl)-6-azauracil (**3e**).

Yield 82%; mp 138 - 139 °C (CH_2Cl_2 and MeOH); UV: λmax (log ε) 291 (3.55) (0.1N HCl), 296 (3.62) (H_2O), 288 (3.67) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6) δ 3.35 (m, 2H, NCH_2), 3.77 (m, 3H, OCH_2 & OCH), 5.69 (m, 2H, 3'-OH & 2'-OH); ^{13}C-NMR (DMSO-d_6) δ 54.08 (C-1'), 63.52 (C-3'), 68.87 (C-2'), 128.10 (C-5), 149.09 (C-2), 154.26(C-4); MS: *m/z* 266 (M^+), 268 $(M+2)^+$; Anal. Calcd for $C_6H_8BrN_3O_4$: C, 27.09; H, 3.03; N, 15.79. Found: C, 27.10; H, 3.04; N, 15.80.

1-(2-Chloro-3-hydroxypropyl)-6-azauracil (**4a**).

6-Azauracil (**1a**, 1.13 g, 10 mmol), HMDS (25 ml), and chlorotrimethylsilane (0.1 ml) were heated under reflux with the exclusion of moisture until a clear solution was obtained. Excess HMDS was evaporated to give the residual oil which was dissolved in dry CH_2Cl_2 (25 ml) and cooled to 0 °C. To this solution was added epichlorohydrin (0.93 g, 10 mmol) in dry CH_2Cl_2 (15 ml) and the resulting reaction mixture was allowed to stir at 0 °C, $SnCl_4$ (0.76 ml, 6.5 mmol) was added slowly and the reaction was continued for 2 h (monitored by TLC). Methanol (20 ml) was added to quench the reaction and the organic solvent was evaporated to give an residual solid which was crystallized from ethanol to afford **4a** (1.16 g; 56%). mp 140 - 141 °C; IR (KBr) cm^{-1}: 600 (C-Cl), 3200, 3500 (OH); UV: λmax (log ε) 282 (3.31) (0.1N HCl), 280 (3.33) (H_2O), 278 (3.41) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6) δ 3.86 (m, 2H, NCH_2), 3.93 (m, 3H, ClCH & OCH_2), 5.42 (br, 1H, 3'-OH), 7.46 (s, 1H, H-5), 12.13 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 47.29 (C-1'), 53.31 (C-3'), 67.67 (C-2'), 135.34 (C-5), 148.46 (C-2), 157.14 (C-4); MS: *m/z* 205 $(M-1)^+$; Anal. Calcd for $C_6H_8ClN_3O_3$: C, 35.05; H, 3.92; N, 20.44. Found: C, 35.06; H, 3.93; N, 20.33.

1-(3-Chloro-2-trimethylsilyloxypropyl)-6-azauracil (**5a**).

6-azauracil (**1a**, 1.13 g, 10 mmol) was suspended in HMDS (25 ml) and then a catalytic amount of chlorotrimethylsilane (0.1 ml) was added. The mixture was heated under reflux with the exclusion of moisture until a clear solution was obtained (*ca.* 4 h). Excess HMDS was removed under reduced pressure to give silylated intermediate as an oil which was dissolved in dry benzene (25 ml). To this stirred solution was added epichlorohydrin (1.11 g, 12 mmol). The reaction mixture was refluxed for 24 h (monitored by TLC). The solvent was evaporated to give the crude product which was purified by silica gel chromatography using a mixed solvent of $CHCl_3$: MeOH (30 :1) to afford **5a** (1.35 g; 49%). mp 109 - 110 °C; IR (KBr) cm^{-1}: 600 (C-Cl), 950 (OSi); UV: λmax (log ε) 277 (3.57) (0.1N HCl), 275 (3.52) (H_2O), 283 (3.63) (0.1N NaOH); ^{1}H-

NMR ($CDCl_3$) δ 0.10 (s, 9H, $OSi(CH_3)_3$), 3.50 (d, 2H, CH_2Cl), 4.10 (d, 2H, NCH_2), 4.11 (m, 1H, OCH), 7.34 (s, 1H, H-5), 10.26 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ -0.01 (CH3), 43.73 (C-3'), 46.91 (C-1'), 69.34 (C-2'), 135.35 (C-5), 149.77 (C-2), 156.20 (C-4); MS: *m/z* 241 (M^+-HCl), 228 (M^+-CH_2Cl); Anal. Calcd for $C_9H_{16}ClN_3O_3Si$: C, 38.91; H, 5.81; N, 15.13. Found: C, 38.80; H, 5.80; N, 15.28.

1-(3-Chloro-2-hydroxypropyl)-6-azauracil (**6a**).

A solution of **5a** (0.28 g, 1 mmol) in 3N HCl (5 ml) was stirred at room temperature for 20 min. The solvent was then evaporated to give a residual solid which was crystallized from H_2O to give **6a** (0.17 g; 83%). mp 146 - 147 °C; IR (KBr) cm^{-1}: 600 (C-Cl), 3250, 3400 (OH); UV: λmax (log ε) 278 (3.39) (0.1N HCl), 278 (3.31) (H_2O), 283 (3.61) (0.1N NaOH); ^{1}H-NMR ($CDCl_3$) δ 3.63 (d, 2H, CH_2Cl), 3.71 (m, 1H, OCH), 3.96 (d, 2H, NCH_2), 5.42 (d, 1H, OH), 7.48 (s, 1H, H-5), 12.51 (br s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 42.77 (C-3'), 47.76 (C-1'), 66.86 (C-2'), 134.74 (C-5), 149.36 (C-2), 156.57 (C-4); MS: *m/z* 169 (M^+-HCl), 156 (M^+-CH_2Cl); Anal. Calcd for $C_6H_8ClN_3O_3$: C, 35.05; H, 3.92; N, 20.44. Found: C, 35.09; H, 3.94; N, 20.34.

1-(3-benzyloxy-2-hydroxypropyl)-6-azaisocytosine (**8**).

6-azaisocytosine (**7**, 1.12 g, 10 mmol) was silylated and then alkylated as described for the preparation of **2a**. The crude product was eluted in a silica gel column with a mixed solvent of $CHCl_3$ and MeOH (20:1) and the proper fractions were combined and evaporated to give **8** (1.29 g, 47 % yield). mp 154-155 °C; ^{1}H-NMR (DMSO-d_6): δ 3.43 (m, 2, NCH_2), 3.90 (m, 3, OCH & OCH_2), 4.47 (s, 2, Ar-CH_2), 5.33 (br s, 1, 2'-OH), 7.09 (s, 2, NH2), 7.22 (s, 1, H-5), 7.29 (m, 5, Ar); ^{13}C-NMR (DMSO-d_6): δ 55.92 (C-1'), 67.49 (C-2'), 71.94 (C-3'), 72.48 (Ar-C), 139.78 (C-5), 156.35 (C-2), 163.29 (C-4); MS: *m/z* 277 $(M+1)^+$; Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.44; H, 5.78; N, 20.25.

1-(2,3-Dihydroxypropyl)-6-azaisocytosine (**9**).

Compound **9** was prepared by the same procedure as **3a** in 79% yield (from **8**, method A) and 57% yield (from **7**, method B) respectively. mp 209-210 °C (CH_2Cl_2 and MeOH); UV: λmax (log ε): 278 (3.51) (0.1N HCl), 278 (3.40) (H_2O), 276 (3.17) (0.1N NaOH); ^{1}H-NMR (DMSO-d_6): δ 3.42 (m, 2, NCH_2), 3.87 (m, 3, OCH & OCH_2), 4.85 (t, 1, 3'-OH), 5.25 (d, 1, 2'-OH), 7.18 (s, 2, NH_2), 7.28 (s, 1, H-5); ^{13}C-NMR (DMSO-d_6): δ 55.60 (C-1'), 62.91 (C-3'), 69.16 (C-2'), 139.31 (C-5), 156.01 (C-2), 162.94 (C-4); MS: *m/z* 187 $(M+1)^+$; Anal. Calcd for $C_6H_{10}N_4O_3$: C, 38.71 ; H, 5.41; N, 30.09. Found: C, 38.64 ; H, 5.46 ; N, 29.96.

1-(2-Chloro-3-hydroxypropyl)-6-azaisocytosine (**10**).

Compound **10** was prepared from compound **7** by the same procedure as **4a** in 31% yield. mp 175-176 °C (EtOH); UV: λmax (log ε): 285 (3.71) (0.1N HCl), 287 (3.31)

(H_2O), 281 (3.26) (0.1N NaOH); ^{1}H-NMR (DMSO-*d*6): δ 3.61 (m, 2, NCH_2), 4.04 (m, 1, ClCH), 3.83 (m, 2, OCH_2), 5.74 (d, 1, 3'-OH), 7.23 (s, 2, NH2), 7.31 (s, 1, H-5); ^{13}C-NMR (DMSO-*d*6): δ 46.62 (C-1'), 55.40 (C-3'), 67.66 (C-2'), 139.38 (C-5), 155.70 (C-2), 162.82 (C-4); MS: *m/z* 205 (M^+); Anal. Calcd for $C_6H_9ClN_4O_2$: C, 35.22; H, 4.43; N, 27.38. Found: C, 35.22; H, 4.47; N, 27.38.

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