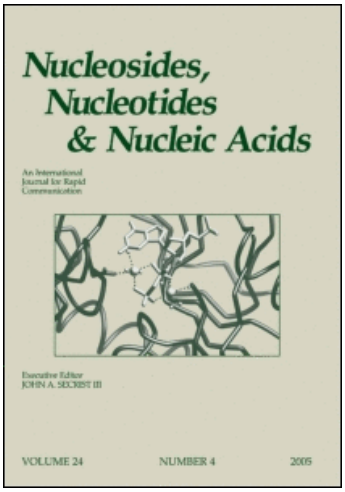

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SYNTHETIC STUDIES ON THE ACYCLIC NUCLEOSIDES OF 5-SUBSTITUTED-6-AZAURACILS

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ABSTRACT A number of acyclic nucleosides have been prepared. 5-substituted-6-azauracils were persilylated with HMDS and then alkylated with aliphatic side chains e.g., (2-acetoxyethoxy)methyl bromide, 1,3-dibenzyloxy-2-chloromethoxypropane, (1-benzyloxy-3-phthalimido-2-propoxy)methyl chloride, and 1-benzyloxy-2-chloromethoxybutane to yield protected acyclic nucleosides which were deprotected by Lewis acid or palladium to give various 6-azauracil acyclonucleosides.

INTRODUCTION

The successful development of the acyclic nucleoside Acyclovir (ACV)[1-4] in 1978 followed by the discovery of its higher antiviral activity than conventional nucleosides, together with an understanding of its antiviral mechanism, has induced general interest in the development and evaluation of acyclic nucleoside analogues for their antiviral activities.

Mechanistically, when ACV enters infected cells, it is first phosphorylated to ACV monophosphate by a virus-specified thymidine kinase. The resulting monophosphate is then converted by cellular enzymes to the corresponding ACV triphosphate which can prevent virus replication by inhibition of the viral DNA polymerase.[5] In the event of ACV being incorporated into the viral DNA chain, its lack of 3'-end structure also leads to chain termination, thus

interrupting viral proliferation. Therefore, ACV displays a high therapeutic index clinically and has become a very effective drug against herpes virus.

The clinical success of ACV has stimulated the synthesis of many analogues in an attempt to search for more potent antiviral drugs. For instance, Ganciclovir (DHPG), an acyclic analogue of 2'-deoxyguanosine that lacks the 2'-carbon, is similar to ACV in the antiviral mechanism. In vitro experiments have showed that both ACV and DHPG are fifty times more effective against herpes simplex virus than ara-A.[6-7] However, in vivo studies using intraperitoneal HSV-1 Murine Encephalitis infected mice, showed that the minimum effective dose for DHPG was only 1/60 of ACV. The discrepency between in vitro and in vivo results has been attributed to the faster in vivo activation of DHPG which enables it to fully function before being catabolized or excreted.

Earlier studies[8-11] discovered that some uracil derivatives displayed a range of biological effects. 6-Azauracil and its ribonucleoside, 6-azauridine, have both antitumor and antiviral activities. 5-Substituted uracil derivatives can act as uridine phosphorylase inhibitors and 5-benzyluracil is an inhibitor of the uridine phosphorylase[12-13] of Walker 256 carcinoma with an inhibition constant, Ki, of 5.3 μ M.

The present investigation presents modifications of both the 5-position and the acyclic sugar moiety of 6-azauracil acyclonucleosides. The 5-position was substituted with different alkyl and aryl groups whereas the acyclo sugar moiety (all of which contained the "5'-OH" group) was modified at the "3'- position" by substitution with various isosteric functions. These compounds were then screened by in vitro studies for antiviral activities.

CHEMISTRY

(2-Acetoxyethoxy)methyl bromide (1), was prepared by reacting 1,3-dioxolane with ice cooled acetyl bromide.[4] 5- Alkyl or aryl substituted 6-azauracil (2a-f)[10,14-15] was refluxed with hexamethyl disilazane (HMDS) and a catalytic amount of chlorotrimethylsilane (TMSCl) for about three hours. The excess HMDS was then evaporated by vacuum distillation to give persilylated intermediate as an oily

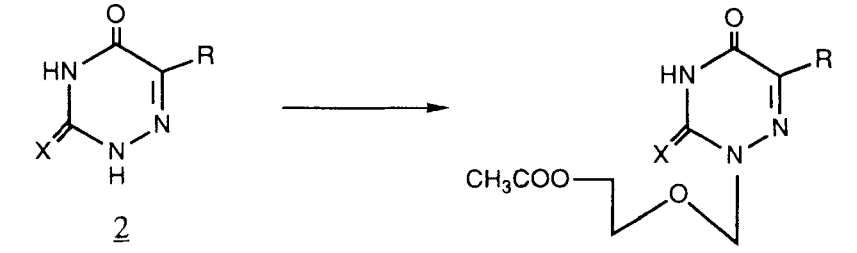
residue which was coupled with 1[4] in dry acetonitrile to afford 1-[(2-acetoxyethoxy)methyl]-6-azauracils (3a-f) as shown in Scheme I. Deacetylation of 3a-f was done by refluxing the coupled compounds in methanolic ammonia for a few hours to give 1-[(2-hydroxyethoxy)-methyl]-6-azauracils (4a-f). Similar reaction conditions leading to the synthesis of certain 6-azauracil acyclonucleosides (analogs of 4) were also previously described.[16-17]

Reaction of epichlorohydrin with benzyl alcohol and sodium hydroxide gave 1,3-dibenzyloxy-2-propanol (5a) which was chloromethylated with paraformaldehyde and dry HCl in dichloromethane at 0℃ to yield 1,3-dibenzyloxy-2-chloromethoxypropane (5b).[18] Each of the persilylated derivatives from 2a-d, prepared as mentioned in the previous section, was glycosylated with one molar equivalent of 5b[10] in dry acetonitrile to give 1-[(1,3-dibenzyloxy-2-propoxy)-methyl]-6-azathymine (6a) as shown in Scheme Ⅱ.

When 2a was glycosylated, in addition to 6a which was obtained as the major and expected product, a minor product was also isolated. The ^{1}H nmr spectrum of this minor product showed two singlets at 5.24 and 5.34 ppm, corresponding to two C1' methylenes. The ^{13}C nmr spectrum also showed two peaks corresponding to the C3' carbon. These results suggested that the minor product was 1,3-bis-[1,3-dibenzyloxy-2-(propoxymethyl)]-6-azathymine (7a). Compounds 6a and 7a were easily separated by silica gel chromatography using a mixed solvent of chloroform and methanol as eluent.

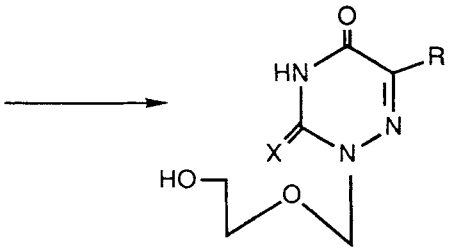
Debenzylation of 6a-d with either boron trichloride[19] in dichloromethane at -78℃ or palladium(Ⅱ) oxide[18] in a mixed solvent of absolute alcohol and cyclohexene afforded the desired 5-substituted 1-[(1,3-dihydroxy-2-propoxy)methyl]-6-azauracils 9a-d.

Attempts to deprotect 6a by using boron tribromide as described in the literature[20] led to the isolation of an unknown major product along with a minor quantity of 9a. The ^{1}H nmr spectrum of the unknown compound contained only three peaks at 2.24, 3.48 and 5.28 ppm, corresponding to aromatic methyl, methoxy and C1' methylene respectively. In the ^{13}C nmr spectrum, only six signals were observed. Three signals appear at δ 157.22, 149.70 and 144.72 ppm were attributed to the ring carbons C5, C3 and C6 of the



2 3

a) X= O, R= CH_3
b) X= O, R= C_6H_5
c) X= O, R= $CH_2C_6H_5$
d) X= S, R= CH_3
e) X= S, R= C_6H_5
f) X= S, R= $CH_2C_6H_5$



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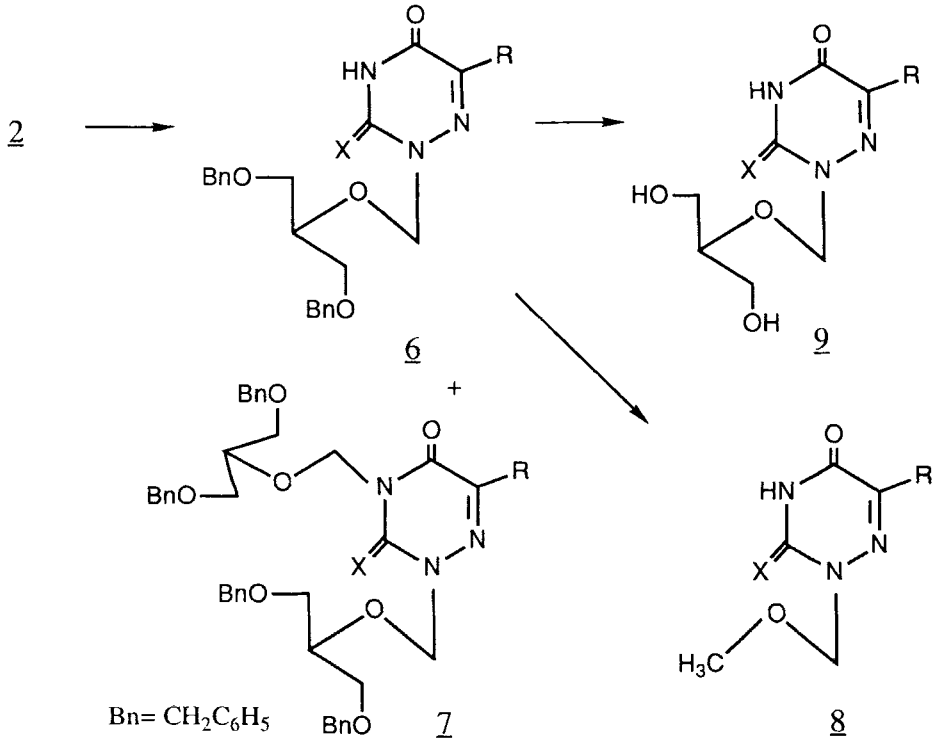
Scheme I



6 9 7 8

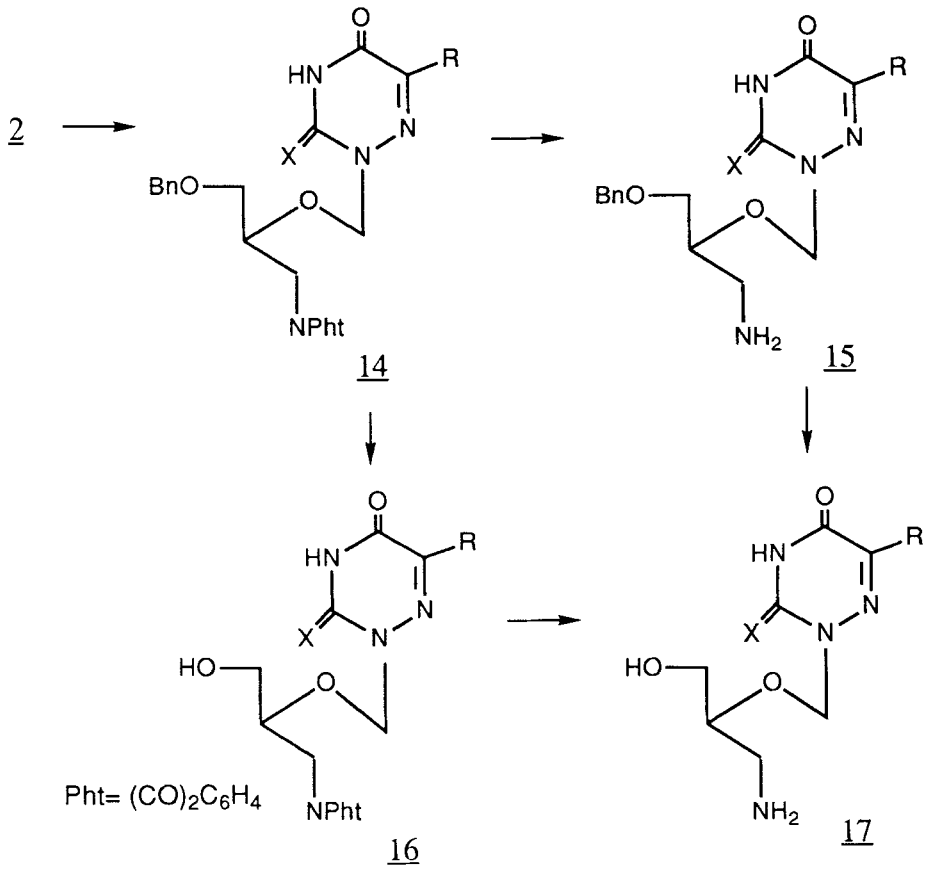
Bn= $CH_2C_6H_5$

Scheme II

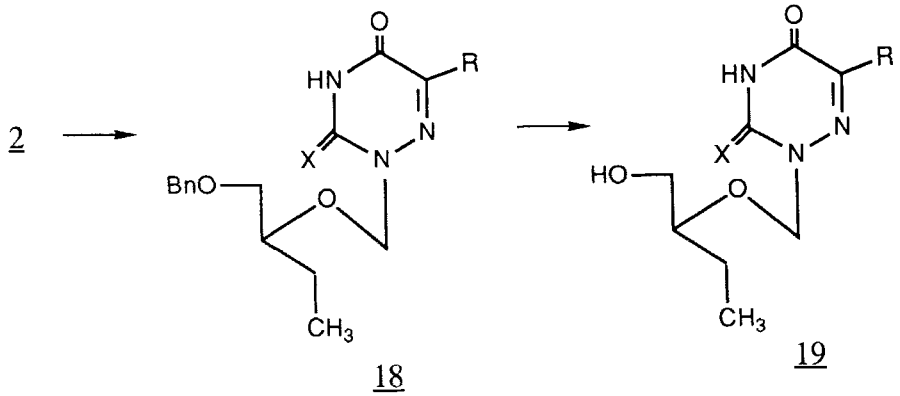
as-triazine, respectively. The other three peaks at δ 80.83, 57.66 and 16.38 ppm were assigned to C1', methoxy, and aromatic methyl, respectively. These results indicated that the major product was 1-(methoxymethyl)-6-azathymine (8a). Complex formation of boron tribromide and the C2 oxygen followed by a nucleophilic substitution may have occurred at C1' ($N-CH_2-O$) when the complex was quenched by the addition of methanol.

The introduction of an amino function into the acyclic sugar moiety started with the treatment of 3-benzyloxypropylene oxide (10)[21] with concentrated aqueous ammonium hydroxide solution (24%), during which 10 underwent S_N2 substitution to give 1-amino-3-benzyloxy-2-propanol (11). Reacting 11 with phthalic anhydride in toluene resulted in the formation of N-(3-benzyloxy-2-hydroxypropyl)phthalimide (12). Chloromethylation of 12 by reaction with paraformaldehyde and dry HCl in 1,2-dichloroethane at 0～5℃ yielded (1-benzyloxy-3-phthalimido-2-propoxy)methyl chloride (13).[18] Alkylation of the persilylated bases 2b-c with 13 in toluene gave 1-[(1-benzyloxy-3-phthalimido-2-propoxy)methyl]-6-azauracils (14b-c) as shown in Scheme Ⅲ. The phthaloyl protecting group of 14b-c was removed with hydrazine in ethanol to form 1-[(1-amino-3-benzyloxy-2-propoxy)methyl]-6-azauracils (15b-c).[22] Attempts to remove the benzyl group of 15b-c by boron trichloride in dichloromethane were not successful due to the poor solubility of 15b-c in nonpolar solvents. Deprotection by PdO catalyzed hydrogenation also failed. Therefore, 15b-c were refluxed with cyclohexene in ethanol with a catalytic amount of $Pd(OH)_2$ to afford 1-[(1-amino-3-hydroxy-2-propyl)methyl]-6-azauracils 17b-c. Alternatively, 14b-c can first be debenzylated with $Pd(OH)_2$[23] to obtain 1-[(1-hydroxy-3-phthalimido-2-propoxy)methyl]-6-azauracils (16b-c) followed by treatment with hydrazine to give 17b-c.

The condensation of the persilylated derivative of 2a with 1-benzyloxy-2-chloromethoxybutane[4] in dry toluene gave 1-[(1-benzyloxy-2-butyloxy)methyl] 6-azathymine (18a) as shown in Scheme Ⅳ. Removal of the benzyl group from 18a to form 1-[(1-hydroxy-2-butoxy)methyl]-6-azathymine (19a) can be achieved either by boron trichloride or by PdO catalyzed hydrogenation.



Scheme III



Scheme IV

The use of amino or methyl functions to replace a hydroxy group in the acyclic sugar moiety is aimed at exploiting the similar stereochemistry and isoelectronic structure of the amino, methyl and hydroxy group, so that a more potent drug with lower host cytotoxic effects could be developed.

BIOLOGICAL SCREENING

The compounds described in this manuscript were tested against HSV-1 and HSV-2 and were found to be inactive.

EXPERIMENTAL

Melting points were determined on a Yanaco micromelting point apparatus and were uncorrected. The ^{1}H and ^{13}C nmr spectra were obtained with a Bruker Analytik WP-100 spectrometer. The chemical shifts are expressed in ppm with respect to tetramethylsilane. Thin layer chromatographic data (R_f values) was recorded from Merck Kieselgel 60 F254 analytical sheets. Column chromatography was performed using Merck silica gel 60 (230-240 mesh) packed in glass columns using 15g of silica per gram of crude material. UV spectra were recorded on a Beckman model 34 UV-visible spectrometer. A Heraeus CHNO analyzer was used for elemental analyses. The elemental analyses data agree within ± 0.4% of the theoretical values for all compounds.

Coupling of 5-alkyl or aryl substituted 6-azauracils (2a-f) with (2-acetoxyethoxy)methyl bromide (1)

Compound 4a (1.5mmole) was silylated using hexamethyldisilazane (5mL) in the presence of a catalytic amount of trimethylsilyl chloride. The stirred mixture was refluxed with the exclusion of moisture. After a clear solution was obtained, the reaction mixture was refluxed for another 3 hours, followed by the removal of excess silylating reagent at reduced pressure. The residue thus obtained, a clear oil, was dissolved in dry acetonitrile (15mL) and cooled to 0 ℃. To this solution, 1.5mmole of 1 (dissolved in 5 mL dry acetonitrile) was added slowly with stirring and allowed to warm to room temperature. The progress of the reaction was monitored by tlc until completion. Volatile materials in the reaction mixture were

again removed at reduced pressure to give a yellow oily product, which was chromatographed to give 3a. The same reaction sequence was adopted to prepare 3b-f.

Compound 3a: yield 62%; m.p. 68-71 ℃; purification (silica gel column MeOH:$CHCl_3$ = 1:20). ^1H nmr ($CDCl_3$): δ 2.08(s, 3H, CH_3COO); 2.28 (s, 3H, CH_3); 3.88(m, 2H, $-OCH_2CH_2O-$); 4.20(m, 2H, $-OCH_2CH_2O-$) and 5.32(s, 2H, $-NCH_2O$).

Compound 3b: yield 87%; purification (silica gel column, ethyl acetate:n-hexane = 2:3, followed by recrystallization from MeOH); m.p. 125-126℃. ^1H nmr ($CDCl_3$): δ 2.05(s, 3H, CH_3COO); 3.87-4.29 (A_2B_2, 4H, $-OCH_2CH_2O-$); 5.46(s, 2H, $-NCH_2O$); 7.36-8.05(m, 5H, 5-Ar) and 10.30(br s, 1H, 3-NH).

Compound 3c: yield 75%; purification (silica gel column, MeOH:$CHCl_3$ = 1:50). ^1H nmr ($CDCl_3$): δ 2.02(s, 3H, CH_3COO); 3.77-4.23(A_2B_2, 4H, $-OCH_2CH_2O-$); 3.89(s, 2H, $5-CH_2Ar$); 5.32(s, 2H, $-NCH_2O$); 7.20(br s, 5H, 5- CH_2Ar) and 10.29(br s, 1H, 3-NH).

Compound 3d: yield 58%; purification (same as 5c). ^1H nmr ($CDCl_3$): δ 2.10 (s, 3H, CH_3COO); 2.30(s, 3H, $5-CH_3$); 3.98(m, 2H, $-OCH_2CH_2O-$); 4.22(m, 2H, $-OCH_2CH_2O-$); 5.72(s, 2H, $-NCH_2$) and 10.98(br s, 1H, 3-NH).

Compound 3e: yield 77%; purification (silica gel column, ethyl acetate:n-hexane = 2:3); m.p. 133℃-136℃. ^1H nmr ($CDCl_3$): δ 2.01 (s, 3H, CH_3COO); 3.96-4.32(A_2B_2, 4H, $-OCH_2CH_2O-$); 5.85(s, 2H, $-NCH_2O$); 7.38-8.13(m, 5H, 5-Ar) and 10.19(br s, 1H, 3-NH).

Compound 3f: yield 61%; purification (silica gel column, MeOH/$CHCl_3$ = 1:60). 1H nmr($CDCl_3$): δ 2.04(s, 3H, CH_3COO); 3.85-4.26 (A_2B_2, 4H, $-OCH_2CH_2O-$); 3.93(s, 2H, $5-CH_2Ar$); 7.28(br s, 5H, $5-CH_2-Ar$) and 10.81(br s, 1H, 3-NH).

Deacetylation of 5-substituted 1-[(2-acetoxyethoxy)methyl]-6-azauracils (3a-f)

A solution of 3a (0.79mmole) in 40 mL of methanolic ammonia (previously saturated at -10℃) was allowed to stand at room temperature for 24 hours in a tightly stoppered flask. The solvent from the reaction mixture was then removed by evaporation, and the resulting gum was dissolved in ethyl acetate, from which 4a crysta-

llized out. The same procedure was used to convert each of the compound 3b-f to the respective 4b-f.

Compound 4a: yield 83%. ^{1}H nmr ($CDCl_3$): δ 2.25(s, 3H, CH_3); 3.76(m, 4H, $-OCH_2CH_2O-$) and 5.31(s, 2H, $-NCH_2O$). ^{13}C nmr ($CDCl_3$): δ 15.86(5-CH_3); 60.03(5'-C); 70.48(4'-C); 78.79(1'-C); 143.39(5-C); 149.02(2-C) and 157.07(4-C). UV λ_{max} (nm): 263(0.1M HCl), 262 (H_2O), 250(0.1M NaOH). Anal. Calcd. for $C_7H_{11}N_3O_4$: C, 41.80; H, 5.51; N, 20.89. Found: C, 41.76; H, 5.52; N, 20.79.

Compound 4b: yield 82%; m.p. 142℃-143℃; purification (recrystallized from ethyl acetate). ^{1}H nmr (DMSO-d_6): δ 3.53-3.66(m, 4H, $-OCH_2CH_2O$); 5.32(s, 2H,$-NCH_2O$) and 7.43-7.93(m, 5H, 5-Ar). ^{13}C nmr (DMSO-d_6): δ 60.34(5'-C); 71.37(4'-C); 79.65(1'-C); 128.29, 128.43, 129.93, 132.10(Ar-C); 141.63(5-C); 148.91(2-C) and 156.79 (4-C). UV λ_{max} (nm): 290.2(0.1M HCl), 289.5 (H_2O), 278.4(0.1M NaOH). Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.81; H, 5.02; N, 15.95.

Compound 4c: yield 78%; purification (silica gel column, MeOH:$CHCl_3$=1:8). ^{1}H nmr ($CDCl_3$): δ 3.68(s, 4H, $-OCH_2CH_2O-$); 3.84(s, 2H, 5-CH_2-Ar); 5.26(s, 2H,$-NCH_2O$) and 7.17(br s, 5H, 5-CH_2-Ar). ^{13}C nmr ($CDCl_3$): δ 35.53(5-CH_2-Ar); 61.06(5'-C); 71.03(4'-C); 79.46 (1'-C); 126.64, 128.24, 128.98, 135.59(Ar-C); 145.78(5-C); 149.04 (2-C) and 156.27(4-C). UV λ_{max} (nm): 264.2(0.1M HCl), 262.6(H_2O), 254.7(0.1M NaOH). Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.23; H, 5.40; N, 15.21.

Compound 4d: yield 77%; purification (silica gel column, MeOH:$CHCl_3$ = 1:10). ^{1}H nmr ($CDCl_3$): δ 2.14(s, 3H, CH_3); 3.58(m, 4H,$-OCH_2CH_2O-$); 5,58(s, 2H,$-NCH_2O$) and 13.12(br s, 1H, NH). ^{13}C nmr ($CDCl_3$): δ 16.35(5-CH_3); 60.25(5'-C); 71.63(4'-C); 83.54(1'-C); 449.28(5-C); 174.67(4-C) and 152.85(2-C). Anal. Calcd. for $C_7H_{11}N_3O_3S$: C, 38.70; H, 5.10; N, 19.34; S, 14.76. Found: C, 38.76; H, 5.12; N, 19.24; S, 14.62.

Compound 4e: yield 71%; m.p. 143℃-144℃; purification (recrystallized from acetone. ^{1}H nmr (DMSO-d_6): δ 3.55-3.78(m, 4H, $-OCH_2CH_2O-$); 4.68(br s, 1H, OH); 5.74(s, 2H, $-NCH_2O$); 7.46-8.01(m, 5H, 5-Ar) and 13.43(br s, 1H,3-NH). ^{13}C nmr (DMSO-d_6): 60.30(5'-C); 71.87(4'-C); 84.06(1'-C); 128.37, 128.58, 130.60, 131.41(Ar-C); 145.71(5-C); 152.23(2-C) and 174.34(4-C). UV λ_{max} (nm): 280.3(0.1M

HCl), 279.8 (H_2O), 278.8(0.1M NaOH). Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04; S, 11.48. Found: C, 51.64; H, 4.76; N, 15.00; S, 11.43.

Compound 4f: yield 69%; m.p. 100℃ -101℃ ; purification (column as for 4c, followed by recrystallization from ethyl acetate). ^1H nmr (DMSO-d_6): δ 3.46-3.64(m, 4H, $-OCH_2CH_2O-$); 3.86(s, 2H, 5-CH_2Ar); 4.68(br s, 1H, OH); 5.61(s, 2H, $-NCH_2O$); 7.27(s, 5H, 5-CH_2-Ar) and 13.33(br s, 1H, 3-NH). ^{13}C nmr (DMSO-d_6): δ 35.42(5-CH_2Ar); 60.22 (5'-C); 71.76(4'-C); 83.61(1'-C); 126.4, 128.54, 129.21, 136.07 (Ar-C); 150.11(5-C); 152.38(2-C) and 174.67(4-C). UV λ_{max} (nm): 272.8 (0.1M HCl), 271.8(H_2O), 267.4(0.1M NaOH). Anal. Calcd. for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32; S, 10.93. Found: C, 53.28; H, 5.18; N, 14.32; S, 10.92.

Coupling of 2a-d with 1,3-Dibenzyloxy-2-chloromethoxypropane (5b)

Compound 5b was reacted with silylated derivatives of 2a-d, as mentioned in the preparation of 3a, to obtain 6a-d. A minor product 7a was also obtained in the preparation of 6a.

Compound 6a: yield 54%; purification (silica gel column, MeOH:$CHCl_3$ = 1:50); ^1H nmr ($CDCl_3$): δ 2.08(s, 3H, 5-CH_3); 3.50(d, 4H, 3', 5'-$OCH_2CH<$); 4.15(dd, 1H, 4'-CH); 4.41(s, 4H, OCH_2Ar); 5.38 (s, 2H, 1'-NCH_2O); 7.21(m, 10H, Ar) and 10.45(br s, 1H, 3-NH).

Compound 7a: yield 10%; ^1H nmr ($CDCl_3$): δ 2.02(s, 3H, 5-CH_3); 3.44(d, 2H, 1'-N_3CH_2O-); 4.15(m, 1H, 4'-CH); 4.39(s, 4H, $-OCH_2Ar$); 5.34(d, 2H, 1'-N_1CH_2O-) and 7.23(M, 10H, OCH_2Ar).

Compound 6b: yield 83%; purification (silica gel column, MeOH:$CHCl_3$ = 1:30); ^1H nmr ($CDCl_3$): δ 3.55(d, 4H, 3',5'-$OCH_2CH<$); 4.24(m, 1H, 4'-CH), 4.47(s, 4H, CH_2Ar); 5.53(s, 2H, 1'-NCH_2O); 7.23-8.06(m, 15H, all Ar) and 10.16(br s, 1H, 3-NH).

Compound 6c: yield 77%; purification (silica gel column, MeOH:$CHCl_3$ =1:50); ^1H nmr ($CDCl_3$): δ 3.50(d, 4H, 3',5'-$OCH_2CH<$); 3.82(s, 2H, 5-CH_2Ar); 4.14(m, 1H, 4'-CH); 4.43(s, 4H, OCH_2Ar); 5.41 (s, 2H, 1'-NCH_2O); 7.24(br s, 15H, all Ar) and 9.65(br s, 1H,3-NH).

Compound 6d: yield 53%; purification (silica gel column, MeOH :$CHCl_3$ = 1:20); ^1H nmr (DMSO-d_6): δ 2.10(s, 3H, 5-CH_3); 3.48(m, 4H, 3',5'-$OCH_2CH<$); 3.70(m, 1H, 4'-CH) and 5.70(s, 2H, 1'-NCH_2O-).

Preparation of 1-(methoxymethyl)-6-azathymine (8a)

To a solution of 1-[(1,3-dibenzyloxy-2-propoxy)methyl]-6-azathymine (6a, 0.82g) in dichloromethane (10mL) was added boron tribromide in dichloromethane (4mL, 1M solution). The mixture was stirred under nitrogen at -78℃ for 40 minutes and then quenched by the addition of methanol (30 mL), warmed to room temperature and evaporated under reduced pressure. The residue thus obtained was chromatographed on a silica gel column using a mixed solvent of chloroform and methanol (20:1) as an eluent to give 0.24g (68% yield) of 8a. ^{1}H nmr ($CDCl_3$): δ 2.24(s, 3H, 5-CH_3); 3.48(s, 3H, OCH_3) and 5.28(s, 2H, -N-CH_2-O). ^{13}C nmr ($CDCl_3$): δ 16.38(5-CH_3); 57.66(3'-C); 80.83(1'-C); 144.72(5-C); 149.70(2-C) and 157.22(4-C). Anal. Calcd. for $C_6H_8N_2O_3$: C, 42.11; H, 5.30; N, 24.55. Found: C, 42.21; H, 5.33; N, 24.50.

Removal of benzyl groups from 1-[(1,3-dibenzyloxy-2-propoxy)methyl] 6-azauracils (6a-c) by PdO(Ⅱ)

The dibenzyl derivative (6a-c, 1g) was placed in a 25mL flask with the addition of 10mL of ethanol, 3mL cyclohexene and 200mg of freshly prepared PdO. The reaction mixture was stirred continuously until tlc showed only one product present. The solution was then filtered and the filtrate was evaporated to dryness at reduced pressure. The crude product was purified by either recrystallization from ethanol or column chromatography.

Compound 9a: yield 95%. ^{1}H nmr (DMSO-d_6): δ 2.10(s, 3H, CH_3); 3.42(d, 4H, 2 -OCH_2-CH<); 5.30(s, 2H,-NCH_2O); 3.48(m, 1H, CH); and 11.90(br s, 1H, -NH). ^{13}C nmr (DMSO-d_6): δ 15.83(5-CH_3); 61.01 (5'-C); 78.37(1'-C); 80.82(4'-C); 143.14(5-C); 148.96(2-C) and 157.12(4-C). UV λ_{max}(nm): 262(0.1M HCl), 262 (H_2O), 250(0.1M NaOH). Anal. Calcd. for $C_8H_{12}N_2O_5$: C, 41.56; H, 5.67; N, 18.17. Found: C, 41.42; H, 5.61; N, 18.22.

Compound 9b: yield 79%; m.p. 142℃-144℃; purification (silica gel column, MeOH:$CHCl_3$ =1:10, followed by recrystallization from ethyl acetate). ^{1}H nmr (DMSO-d_6): δ 3.34-3.77(m, 5H, 4' and 5'-H); 4.60(br s, 2H, 5'-OH); 5.39(s, 2H, -NCH_2O); 7.37-7.95(m, 5H, 5-Ar) and 12.29(br s, 1H, 3-NH). ^{13}C nmr (DMSO-d_6): δ 61.30(5'-C); 79.15 (1'-C); 81.46(4'-C); 129.29, 129.40, 129.88, 132.17(Ar-C); 141.45

(5-C); 148.84(2-C) and 158.81(4-C). UV λ_{max} (nm): 290.9(0.1M HCl), 289.6(H_2O), 278.6 (0.1M NaOH). Anal. Calcd. for $C_{13}H_{15}N_3O_6$: C, 53.24; H, 5.16; N, 14.33. Found: C, 52.94; H, 5.20; N, 14.15.

Compound 9c: yield 81%; m.p. 106-107℃ ; purification (silica gel column, MeOH:$CHCl_3$ = 1:1, followed by recrystallization from ethanol). ^1H nmr (DMSO-d_6): δ 3.40-4.70(m, 5H, 3' and 5'H); 3.82 (s, 2H, 5-CH_2Ar); 4.58(br s, 2H, 5'-OH); 5.28(s, 2H, -NCH_2O); 7.27 (s, 5H, 5- CH_2Ar) and 12.20(br s, 1H, 3-NH). ^{13}C nmr (DMSO-d_6) δ 35.48(5-CH_2Ar); 61.26(5'-C); 78.76(1'-C); 81.20(4'-C); 126.74, 128.58, 129.09, 136.67(Ar-C); 144.87(5-C); 149.12(2-C) and 156.98 (4-C). UV λ_{max}(nm): 264.7(0.1M HCl), 261.9(H_2O), 253.9(0.1 M NaOH). Anal. Calcd. for $C_{14}H_{17}N_3O_6$: C, 54.72; H, 5.58; N, 13.67. Found: C, 54.60; H, 5.62; N, 13.66.

Removal of benzyl group from 6d by boron trichloride

To 2 g of the dibenzyl compound (6d), in dry dichloromethane (25mL), was added boron trichloride in dichloromethane (5mL, 1M solution). The mixture was stirred under nitrogen at -78℃ for 2 hours, after which an additional 5mL of the boron trichloride solution was added. Stirring was continued for another one hour, at which point 50mL of 1:1 methanol and dichloromethane mixture was added. The solution was allowed to warm to room temperature, filtered, and solvents in the filtrate removed under reduced pressure. The residue obtained, a syrup, was chromatographed on a silica gel column to yield compound 9d.

Compound 9d: yield 53%; purification (silica gel column MeOH: $CHCl_3$ = 1:20). ^1H nmr (DMSO-d_6): δ 2.10(s, 3H, CH_3); 3.48(m, 4H, 2 -$OCH_2CH<$); 3.70(m, 1H, CH) and 5.70(s, 2H, -NCH_2). ^{13}C nmr (DMSO-d_6): δ 16.40(5-CH_3); 61.25(5'-C); 81.47(1'-C); 83.26(4'-C); 149.26 (5-C); 153.11(2-C) and 174.62(4-C). Anal. Calcd. for $C_8H_{13}N_3O_4S$: C, 38.86; H, 5.30; N, 16.99; S, 12.97. Found: C, 38.88; H, 5.32; N, 16.74; S, 12.71.

Preparation of 1-[(1-benzyloxy-3-phthalimido-2-propoxy)methyl]-6-azauracils (14b,c)

Compounds 2b and 2c were coupled with (1-benzyloxy-3-phthalimido-2-propoxy)methyl chloride (13), using the same procedure for the coupling of compounds 1 and 2a to obtain 14b and 14c.

Compound 14b: yield 74%; m.p. 162-165℃ ; purification (silica gel column, MeOH:$CHCl_3$ = 1:70, followed by recrystallization from ethanol); ^1H nmr ($CDCl_3$): δ 3.60-3.97(m, 4H, 5' and 3'- H); 4.57(s, 2H, OCH_2Ar); 4.66(m, 1H, 4'-CH); 5.40 and 5.50(two d, 2H, 1'-NCH_2O), 7.25-7.91(m, 14H, all Ar) and 10.00(br s, 1H, 3-NH).

Compound 14c: yield 63%; m.p. 132-135℃ ; purification (same as for 14b); ^1H nmr ($CDCl_3$): δ 3.50-3.89(m, 4H, 5' and 3'-H); 3.63(s, 2H, 5-CH_2Ar); 4.34(m, 1H, 4'-CH); 4.49(s, 2H, OCH_2Ar); 5.34(s, 2H, 1'-NCH_2O); 7.16-7.26(br s, 10H, 5-CH_2Ar and OCH_2Ar); 7.56-7.69(m, 4H, NPhth) and 10.09(br s, 1H, 3-NH).

Deprotection of the phthalimido group of 14b,c.

To 7.8 mmole of 14b dissolved in 150mL of ethanol was added 15mL of hydrazine monohydrate. The mixture was heated under reflux for 3 hours, cooled to room temperature and filtered. The filtrate was concentrated by evaporation and then 200mL of $CHCl_3$ was added. The solution was then washed with 3 x 50mL of 1M aqueous NaOH. After the removal of remaining solvent from the organic layer, the product 15b was recrystallized from ethyl acetate, yield 85%; m.p. 183-184℃ ; ^1H nmr (DMSO-d_6): δ 2.71(dd, 1H, -CH_2NH_2); 2.86(dd, 1H, -CH_2NH_2); 3.52(m, 2H, 5'-CH_2O); 3.97(m, 1H, 4'-CH); 4.47(s, 2H, OCH_2Ar); 4.82(br s, 2H, 3'-NH_2); 5.33 and 5.43 (two d, 2H, 1'-NCH_2-O); 7.32(s, 5H, OCH_2Ar) and 7.39-7.94(m, 5H, 5-Ar).

Compound 15c: yield 79%; m.p. 82-84℃ ; purification (silica gel column, MeOH/ethyl aceate = 1:1, followed by recrystallization from ethyl acetate); ^1H nmr (DMSO-d_6): δ 2.68(dd, 1H, CH_2NH_2); 2.84 (dd, 1H, CH_2NH_2); 3.45(m, 2H, 5'-CH_2O); 3.75(s, 2H, 5-CH_2Ar); 3.90 (m, 1H, 4'-CH); 4.44(s, 2H, OCH_2Ar); 4.88(br s, 2H, 3'-NH_2); 5.20 and 5.30 (two d, 1H, 1'-NCH_2O) and 7.21-7.32(m, 10H, 5-CH_2Ar and OCH_2Ar).

Deprotection of the benzyl group of 14b.

Compound 14b (2 mmole) was dissolved in a mixture of ethanol (12mL) and cyclohexene (3mL), followed by the addition of 30mg of PdO catalyst. The mixture was refluxed for 2 hours and filtered hot to remove the catalyst. The filtrate was evaporated to 5mL and cooled to allow the product 16b to crystallize. Compound 16b was

purified by recrystallization from ethanol. Yield 98%; m.p. 209-212℃ ; ^{1}H nmr (DMSO-d_6): δ 3.42-3.78(m, 5' and 3'-H); 4.13(m, 1H, 4'-CH); 5.02(br s, 1H, 5'-OH); 5.16 and 5.35(two d, 2H, 1'-NCH_2O); 7.38-7.89(m, 9H, 5Ar and Phth) and 12.09(br s, 1H, 3-NH).

Preparation of 1-[(1-amino-3-hydroxy-2-propoxy)methyl]-5-aryl-6-azauracil (17b,c).

Compound 17b was obtained by either (i) deprotecting the hydroxy group of 15b using the same procedure for preparing 16b (reflux for 17 hours, yield 94%) or (ii) deprotecting the amino protecting group of 16b using the same procedure for preparing 15b (yield 88%).

Compound 17b: m.p. 200-202℃. ^{1}H nmr (DMSO-d_6): δ 2.84(m, 2H, 3'-CH_2N); 3.46(d, 2H, 5'-CH_2O); 3.78(m, 1H, 4'-H); 5.23(br s, 3H, NH_2 and OH); 5.32(s, 2H,-NCH_2O) and 7.34-7.69(m, 5H, 5-Ar). ^{13}C nmr (DMSO-d_6): δ 41.3(3'-C); 61.4(5'-C); 78.0(4'-C); 79.3(1'-C); 127.9, 128.4, 128.9, 133.7(Ar-C); 141.5(5-C); 153.4(2-C) and 161.7(4-C). UV λ_{max} (nm): 291.1(0.1MHCl), 281.6(H_2O), 279.3(0.1M NaOH). Anal. Calcd. for $C_{13}H_{16}N_4O_4$: C,53.42; H, 5.52; N, 19.17. Found: C, 53.20; H, 5.60; N, 18.96.

Compound 17c: purification (silica gel column, MeOH:ethyl acetate =1:1). ^{1}H nmr (DMSO-d_6): δ 2.66(dd,1H, CH_2NH_2); 2.72(dd, 1H, CH_2NH_2); 3.41(d,2H, CH_2OH); 3.68-3.74(m, 3H, 4'-H and 5-CH_2Ar); 5.16(br s, 3H, NH_2 and OH); 5.19 and 5.27(two d, 2H,NCH_2O) and 3.74 (s,5H,5-CH_2Ar). ^{13}C nmr(DMSO-d_6): δ 35.8(5-CH_2Ar); 41.4(3'-C); 61.4 (5'-C); 78.1(4'-C); 79.1(1'-C); 145.0(5-C); 153.9(2-C) and 162.2 (4-C). UV λ_{max}(nm): 260.8(0.1M HCl), 257.8(H_2O), 254.4 (0.1M NaOH). Anal. Calcd. for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.92; H, 5.90; N, 18.19.

Preparation of 1-[(1-hydroxy)butoxymethyl]-6-azathymine (19a).

The silylated derivative of 2a was coupled with 1-benzyloxy-2-chloromethoxybutane using the same procedure described for the preparation of 3a to obtain 18a. Catalytic hydrogenation of 18a yielded 19a (82%). 1H nmr ($CDCl_3$): δ 0.90(t, 3H, CH_2CH_3); 1.49 (dq, 2H, CH_2CH_3); 3.60(s, 2H,-$OCH_2CH<$); 3.60(m, 1H, -CHO-); 5.38(s, 2H, -NCH_2O) and 10.60(br s, 1H, -NH). ^{13}C nmr (DMSO-d_6): δ 9.73(3'-

CH_3); 16.18(5-CH_3); 24.12(3'-C); 64.61(5'-C); 79.06(1'-C); 81.77 (4'-C); 144.69(5-C); 149.63(2-C) and 157.02(4-C). UV λ_{max}(nm): 262 (0.1M HCl), 262(H_2O), 250(0.1M NaOH). Anal. Calcd. for $C_9H_{15}N_3O_4$: C, 47.16; H, 6.60; N, 18.33. Found: C, 47.08; H, 6.52; N, 18.12.

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