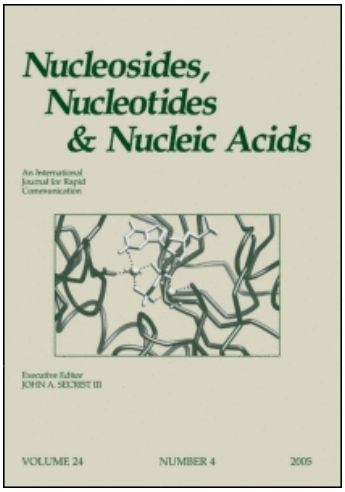

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Synthetic and Antiviral Studies on Certain Acyclic Nucleosides of 5-Benzyl-6-Azauracil Derivatives

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SYNTHETIC AND ANTIVIRAL STUDIES ON CERTAIN ACYCLIC NUCLEOSIDES OF 5-BENZYL-6-AZAURACIL DERIVATIVES

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Abstract

Several 5-(4-substituted benzyl)-6-azauracils have been synthesized from the corresponding benzaldehydes. The 5-benzyl-6-azauracils were silylated with hexamethyldisilazane and then glycosylated with aliphatic halides, e.g., (2-acetoxyethoxy)methyl bromide and 1,3-dibenzyloxy-2-chloromethoxypropane, to give protected acyclic nucleosides which were deprotected to afford acyclonucleosides of 5-(4-substituted benzyl)-6-azauracils. None of the compounds exhibited significant antiviral activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro.

Introduction

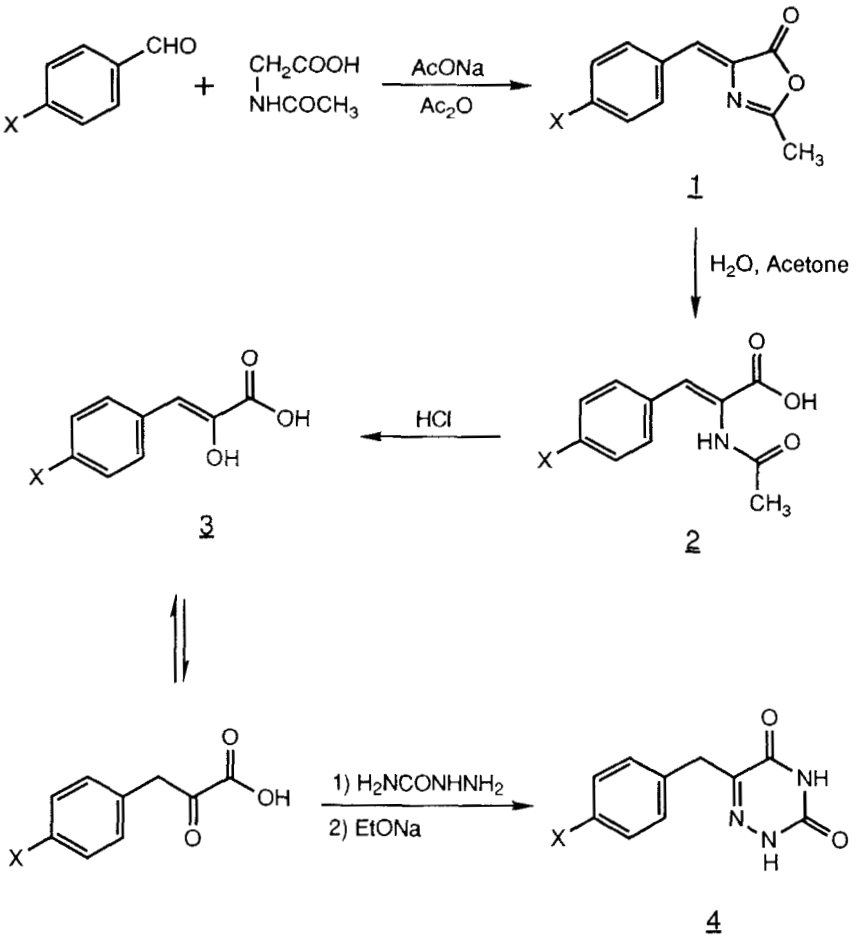
Studies on the aza analogues of purine and pyrimidine have attracted the attention of numerous laboratories mainly because such agents have shown a wide spectrum of chemotherapeutic and biological properties. 8-Azaguanine, an analogue of guanine in which the C8 carbon atom has been replaced by a nitrogen atom, was one of

the first modified purines to display notable carcinostatic effects against murine malignancies[1]. Other azapurines such as 2-azaadenine and 2-azahypoxanthine, have long been known to inhibit the growth of both microbial and mammalian cells[2]. 6-Azauracil (1,2,4-triazin-3,5-dione), an isosteric isomer of uracil, has been proved to possess a broad spectrum of biological effects which include antiviral[3-4], antitumor[5-6], and antifungal[7] activities. Its ribonucleoside, 6-azauridine, also exhibits potent antitumor activity[8].

Earlier studies discovered that 1-[(2-hydroxyethoxy)methyl]-5-benzyluracil (BAU) was a potent inhibitor of uridine phosphorylase and a 5-fluoro-2'-deoxyuridine enhancer[9-10]. Chu and Lin et al. have also reported the synthesis of 1-[(1,3-dihydroxy-2-propoxy)methyl]-5-benzyluracil (DHPBU) and other related derivatives[11-13]. DHPBU was found to be a potent inhibitor of uridine phosphorylase isolated from sarcoma 180 cells with a Ki value of 0.098μM and exhibited no apparent cytotoxicity against Sarcoma 180 host cell. The present report describes the synthesis and antiviral evaluation of aza-BAU and aza-DHPBU. Their analogues bearing methoxy,hydroxy, methyl, and chloro substituents at C-4 position of the benzene ring have also been prepared. Other 6-azauracil acyclonucleosides were previously described[14-17].

Chemistry

5-Benzyl-6-azauracils 4a-e with methoxy, hydroxy, methyl, and chloro substituted at 4-position of the benzene ring were prepared as outlined in Scheme 1. Condensation of substituted benzaldehydes with N-acetylglycine provided (Z)-2-methyloxazol-5(4H)-ones 1a-c, which were refluxed with H_2O and acetone to give (Z)-2-acetamido-2-propenoic acids 2a-c[18a]. Hydrolysis to obtain substituted phenylpyruvic acids 3a-c was accomplished by heating 2a-c in 1N HCl aqueous solution[18b]. The ^1H NMR spectrum of phenylpyruvic acids 3a-c showed singlet at 6.38 ppm containing one proton, which were assigned to -CH= proton of the enol form. The spectral data indicated that α-keto acids 3a-c appear as the enol form as described for phenylpyruvic acid and (p-hydroxyphenyl)pyruvic acid[19]. The α-keto acids 3a-e were condensed with semicarbazide to yield the corresponding semicarbazones, which were cyclized by the use of

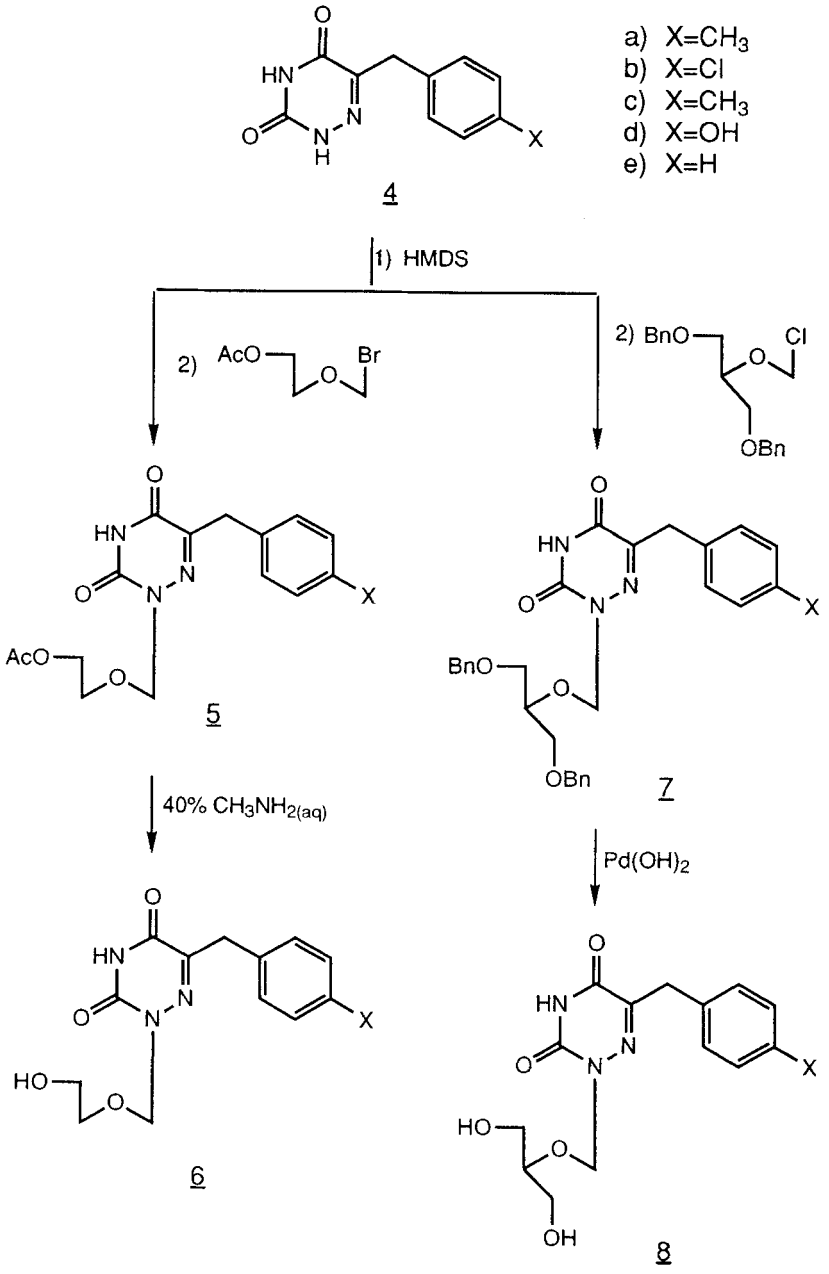


a) X=OCH_3, b) X=Cl, c) X=CH_3

Scheme 1

sodium ethoxide in ethylene glycol to afford substituted 5-benzyl-6-azauracils 4a-e[20-21].

Preparation of the acyclic nucleosides of substituted 5-benzyl-6-azauracils was described in Scheme 2. 5-Benzyl-6-azauracils 4a-e were silylated with hexamethyldisilazane (HMDS) and a catalytic amount of chlorotrimethylsilane (TMSCl) under anhydrous condition. The excess HMDS was then evaporated under diminished pressure to give trimethylsilylated intermediate as an oil in each case.



Scheme 2

Glycosidation of residual oil with (2-acetoxyethoxy)methyl bromide[22] in 1,2-dichloroethane gave 1-[(2-acetoxyethoxy)methyl]-5-benzyl-6-azauracils 5a-e, which were purified by silica gel chromatography. Deacetylation of 5a-e were achieved with 40% aqueous methylamine for a few hours to afford 1-[(2-hydroxyethoxy)methyl]-5-benzyl-6-azauracils 6a-e in a good overall yield.

The persilylated intermediates 4a-e were also glycosidated with 1,3-dibenzyloxy-2-chloromethoxypropane[23] by the same procedure as described for the preparation of 5 to give 1-[(1,3-dibenzyloxy-2-propoxy)methyl]-5-benzyl-6-azauracils 7a-e. Compounds 7a-e were debenzylated with palladium hydroxide[24] to obtain 1-[(1,3-dihydroxy-2-propoxy)methyl]-5-benzyl-6-azauracils 8a-e in a fairly good overall yield.

Antiviral activity

Antiviral and cytotoxicity assays of the new acyclic nucleosides 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 μM.

Experimental Section

Melting points were determined on a Fargo MP-ID melting point apparatus and are uncorrected. Nuclear magnetic resonance (^1H and ^{13}C) spectra were recorded on a Varian Gemini 200 spectrometer. Chemical shifts were expressed in parts per million (δ) with tetramethylsilane (TMS) as an internal standard. Thin-layer chromatography was performed on silica gel 60 F-254 plates purchased from E. Merck and Co.. Column chromatography was performed using Merck silica gel 60 (230-400 mesh) packed in glass columns.

(Z)-4-(4-Methoxybenzylidene)-2-methyloxazol-5(4H)-one (1a).

A mixture of p-anisaldehyde (21.51g, 0.158mol), N-acetylglycine (11.71g, 0.1mol), sodium acetate (6.07g, 0.074mol), and acetic anhydride (25.53g, 0.25mol) was heated at reflux for 10

min. The resulting solution was kept in refrigerator overnight to obtain a solidified mass which was triturated with cold ethanol(40 ml). The resulting yellow crystals were collected and dried to give 11.52g (53%) of 1a. mp: 105-107°C. ^{1}H NMR($CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.95 (d, 2H, aromatic CH, J=8.8 Hz), 7.10 (s, 1H, CH), 8.05 (d, 2H, aromatic CH, J=8.8 Hz).

(Z)-4-(4-Chlorobenzylidene)-2-methyloxazol-5(4H)-one (1b).

Compound 1b was perpared by the same procedure as 1a, the yellow crystals were collected and the excess 4-chlorobenzaldehyde was removed by sublimation to give 12.38g (56%) of 1b which was used in next reaction without further purification. ^{1}H NMR($CDCl_3$): δ 2.42 (s, 3H, CH_3), 7.09 (s, 1H, CH), 7.42 (d, 2H, aromatic CH, J=8.6 Hz), 8.03 (d, 2H, aromatic CH, J=8.4 Hz).

(Z)-4-(4-Methylbenzylidene)-2-methyloxazol-5(4H)-one (1c).

Compound 1c was perpared by the same procedure as 1a in 83% yield. ^{1}H NMR($CDCl_3$): δ 2.39 (s, 6H, $2XCH_3$), 7.12 (s, 1H, CH), 7.24 (d, 2H, aromatic CH, J=8.1 Hz), 7.97 (d, 2H, aromatic CH, J=8.2 Hz).

(Z)-2-Acetamido-3-(4-methoxyphenyl)-2-propenoic acid (2a).

Oxazol-5(4H)-one 1a (10.85g, 50mmol), acetone (85ml), and H_2O (70ml) were refluxed for 6 h. The solvent was evaporated to give a residual solid which was crystallized with water to give 10.66g (91%) of 2a. mp: 220-221°C. ^{1}H NMR(DMSO-d_6): δ 1.98 (s, 3H,CH_3), 3.79 (s, 3H, OCH_3), 6.98 (d, 2H, aromatic CH, J=8.8Hz), 7.23 (s,1H, benzylic CH), 7.60 (d, 2H, aromatic CH, J=9.0 Hz), 9.37 (br s, 1H, NH),12.53 (br, 1H, acidic OH).

(Z)-2-Acetamido-3-(4-chlorophenyl)-2-propenoic acid (2b).

Compound 2b was prepared by the same procedure as 2a in 86% yield. mp: 222°C. ^{1}H NMR(DMSO-d_6): δ 1.98 (s, 3H, CH_3), 7.19 (s, 1H, benzylic CH), 7.47 (d, 2H, aromatic CH, J=8.6Hz), 7.62 (d, 2H, aromatic CH, J=8.6Hz), 9.51 (br s, 1H, NH), 12.78 (br, 1H, acidic OH).

(Z)-2-Acetamido-3-(4-methylphenyl)-2-propenoic acid (2c).

Compound 2c was prepared by the same procedure as 2a in 82% yield. mp: 214-216°C. ^{1}H NMR(DMSO-d_6): δ 1.97 (s, 3H, CH_3), 2.13 (s,

3H, CH_3), 7.19 (s, 1H, benzylic CH), 7.21 (d, 2H, aromatic CH, J=7.9Hz), 7.51 (d, 2H, aromatic CH, J=8.0Hz), 9.41 (br s, 1H, NH), 12.60 (br, 1H, acidic OH).

4-Methoxyphenylpyuvic acid (3a).

Compound 2a (5.88g, 25mmol), 1N HCl aqueous solution(150ml), and ethanol (150ml) were refluxed for 20 h, The undissolved material was filtered off and the filtrate was cooled. The precipitate was collected and dried in a vacuum desiccator to yield 3.54g (73%) of 3a. mp: 165°C. ^{1}H NMR(DMSO-d_6): δ 3.75 (s , 3H, OCH_3), 6.38 (s, 1H, benzylic CH), 6.92 (d, 2H, aromatic CH, J=8.8Hz), 7.71 (d, 2H, aromatic CH, J=8.8Hz), 8.99 (br s, 1H, α-OH), 13.04 (br, 1H, acidic OH).

4-Chlorophenylpyruvic acid (3b).

Compound 3b was perpared by the same procedure as 3a in 68% yield. mp: 171°C. ^{1}H NMR (DMSO-d_6): δ 6.39 (s, 1H, benzylic CH), 7.40 (d, 2H, aromatic CH, J=8.6Hz), 7.78 (d, 2H, aromatic CH, J=8.7Hz), 9.48 (br s, 1H, α-OH), 13.28 (br, 1H, acidic OH).

4-Methylphenylpyruvic acid (3c).

Compound 3c was perpared by the same procedure as 3a in 63% yield. mp: 156-158°C. ^{1}H NMR (DMSO-d_6): δ 2.29 (s, 3H, CH_3), 6.37 (s, 1H, benzylic CH), 7.15 (d, 2H, aromatic CH, J=8.0Hz), 7.64 (d, 2H, aromatic CH, J=8.2Hz), 9.06 (br s,1H, α-OH), 13.07 (br,1H, acidic OH).

5-(4-Methoxybenzyl)-6-azauracil (4a).

Semicarbazide hydrochloride (4.01g, 36mmol) and sodium acetate (5.91g, 72mmol) were dissolved in H_2O (50ml) and to which 4-methoxyphenylpyruvic acid 3a (4.66g, 24mmol) in ethanol (50ml) was added, The solution was stirred for 3 h at room temperature, then acidified with conc. HCl to pH2 in ice-bath. The precipitate was collected and dried in vacuum desiccator for 6 h to give 4-methoxyphenylpyruvic acid semicarbazone (6.44g).

Semicarbazone (6.44g) was added to a solution of sodium ethoxide (1.66g, 72mmol of metal sodium in 40ml anhydrous ethanol)

and ethylene glycol (40ml) and then refluxed for 18 h. The solvent was evaporated to dryness under reduced pressure, the residue was dissolved in hot water (40ml) and the solution was adjusted to pH2 with conc. HCl. The resulting precipitate was collected and crystallized with methanol to give 4.25g (76%) of 4a as white crystal. mp: 210°C. ^{1}H NMR (DMSO-d_6): δ 3.70 (s, 5H, OCH_3 & benzylic CH_2), 6.84 (d, 2H, aromatic CH, J=8.8Hz), 7.14 (d, 2H, aromatic CH, J=8.7Hz), 11.94 & 12.10 (br s, 2H, 1 & 3-NH). ^{13}C NMR(DMSO-d_6): δ 34.56 (benzylic C), 55.28 (OCH_3), 114.02, 128.96, 130.28, 158.20 (aromatic C), 145.03 (C-5), 149.74 (C-2), 157.28 (C-4).
Anal. Cald. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.76; N, 18.02. Found : C, 56.84; H, 4.80; N, 18.08.

The same procedure was used to convert each of the compounds 3b-e to the respective 4b-e.
5-(4-Chlorobenzyl)-6-azauracil (4b): yield 72%, mp: 205-206°C. ^{1}H NMR(DMSO-d_6) : δ 3.77 (s, 2H, benzylic CH_2), 7.25 (d, 2H, aromatic CH, J=8.6Hz), 7.34 (d, 2H, aromatic CH, J=8.5Hz), 11.96 & 12.12 (br s, 2H, 1 & 3-NH). ^{13}C NMR(DMSO-d_6): δ 34.74 (benzylic C), 128.48, 131.20, 131.40, 136.22 (aromatic C), 144.43 (C-5), 149.71 (C-2), 157.26 (C-4).
Anal. Cald. for $C_{10}H_8ClN_3O_2$: C, 50.54; H, 3.39; N, 17.68. Found : C, 50.49; H, 3.46; N, 17.60.

5-(4-Methylbenzyl)-6-azauracil (4c): yield 69%, mp: 221-224°C. ^{1}H NMR(DMSO-d_6) : δ 2.24 (s, 3H, CH_3), 3.72 (s, 2H, benzylic CH_2), 7.10 (s, 4H, aromatic CH), 11.94 & 12.10 (br s, 2H, 1 & 3-NH). ^{13}C NMR(DMSO-d_6): δ 20.87 (CH_3), 34.99 (benzylic C), 129.11, 129.14, 134.10, 135.70 (aromatic C),144.89 (C-5),149.72 (C-2),157.26 (C-4).
Anal. Cald. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.11; N, 19.34. Found : C, 60.76; H, 5.13; N, 19.26.

5-(4-Hydroxybenzyl)-6-azauracil (4d): yield 68%, mp: 283-285°C (dec). ^{1}H NMR(DMSO-d_6) : δ 3.64 (s, 2H, benzylic CH_2), 6.66 (d, 2H, aromatic CH, J=8.6Hz), 7.02 (d, 2H, aromatic CH, J=8.6Hz), 9.24 (br s, 1H, phenolic OH), 11.92 & 12.08 (br s, 2H, 1 & 3-NH). ^{13}C NMR(DMSO-

d_6): δ 34.57 (benzylic C), 115.37, 127.17, 130.16, 156.20 (aromatic C), 145.14 (C-5), 149.74 (C-2), 157.28 (C-4).
Anal. Cald. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found : C, 54.73; H, 4.17; N, 19.07.

5-benzyl-6-azauracil (4e): yield 89%, mp: 209-211°C. ^{1}H NMR(DMSO-d_6) : δ 3.80 (s, 2H, benzylic CH_2), 7.30 (s, 5H, aromatic CH), 11.93 & 12.12 (br s, 2H, 1 & 3-NH).
Anal. Cald. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.64; N, 20.68. Found : C, 58.96; H, 4.72 N, 20.53.

1-[(2-Acetoxyethoxy)methyl]-5-(4-methoxybenzyl)-6-azauracil (5a).

A mixture of 5-(4-methoxybenzyl)-6-azauracil 4a (1.82g, 7.8mmol), chlorotrimethylsilane (2ml) and hexamethyldisilazane (HMDS, 30ml) was heated at reflux with exclusion of moisture until the solution became clear (ca. 3 h). The excess HMDS was removed under reduced pressure, then the residue was dissolved in 1,2-dichloroethane (15ml), and to which (2-acetoxyethoxy)methyl bromide (1.40g, 7.2mmol) in 1,2-dichloroethane (15ml) was added. The reaction mixture was stirred at room temperature overnight, and then the solvent was evaporated to give crude product which was purified by column chromatography on silica gel (CH_2Cl_2-MeOH, 40:1)to yield 2.14g (85%) of 5a. mp: 84-86°C. ^{1}H NMR($CDCl_3$): δ 2.04 (s, 3H, acetylic CH_3), 3.85 (s, 2H, benzylic CH_2), 3.81-4.22 (A_2B_2, 4H, OCH_2CH_2O), 5.34 (s, 2H, NCH_2O), 6.82 (d, 2H, aromatic CH, J=8.8Hz), 7.24 (d, 2H, aromatic CH, J=8.8Hz), 9.75 (brs, 1H, 3-NH). ^{13}C NMR($CDCl_3$): δ 21.30 (acetylic CH_3), 35.60 (benzylic C), 55.74 (OCH3), 63.70 (C-4'), 68.63 (C-3'), 80.18 (C-1'),114.54, 128.01, 130.79, 159.21 (aromatic C), 146.87 (C-5), 149.40 (C-2), 156.49 (C-4), 171.39 (acetylic CO).
Anal. Cald. for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found : C, 54.89; H, 5.51; N, 11.94.

The same procedure was used to convert each of the compounds 4b-e to the respective 5b-e.

1-[(2-Acetoxyethoxy)methyl]-5-(4-chlorobenzyl)-6-azauracil (5b): yield 80%. mp: 94-95°C. ^{1}H NMR($CDCl_3$): δ 2.05 (s, 3H, acetylic CH_3), 3.81-4.23 (A_2B_2, 4H, OCH_2CH_2O), 3.89 (s, 2H, benzylic CH_2), 5.34 (s, 2H, NCH_2O), 7.26 (s, 4H, aromatic CH), 9.62 (brs, 1H, 3-NH). ^{13}C NMR($CDCl_3$): δ 21.85 (acetylic CH_3), 35.38 (benzylic C), 63.22 (C-4'), 68.28 (C-3'), 79.83 (C-1'), 128.22, 130.67, 133.15, 134.04 (aromatic C), 145.71 (C-5), 148.76 (C-2), 155.90 (C-4), 170.92 (acetylic CO). Anal. Cald. for $C_{15}H_{16}ClN_3O_5$: C, 50.93; H, 4.56; N, 11.88. Found : C, 50.84; H, 4.59; N, 11.85.

1-[(2-Acetoxyethoxy)methyl]-5-(4-methylbenzyl)-6-azauracil (5c): yield 83%. mp: 77-79°C. ^{1}H NMR($CDCl_3$): δ 2.04 (s, 3H, acetylic CH_3), 2.30 (s, 3H, CH_3), 3.81-4.22 (A_2B_2, 4H, OCH_2CH_2O), 3.88 (s, 2H, benzylic CH_2), 5.34 (s, 2H, NCH_2O), 7.09 (s, 2H, aromatic CH, J=7.9Hz), 7.21 (s, 2H, aromatic CH, J=8.1Hz), 9.64 (brs, 1H, 3-NH). ^{13}C NMR($CDCl_3$): δ 21.29 (acetylic CH_3), 21.49 (CH_3), 36.01 (benzylic C), 63.70 (C-4'), 68.62 (C-3'), 80.18 (C-1'), 129.60, 129.79, 132.99, 137.22 (aromatic C), 146.80 (C-5), 149.33 (C-2), 156.43 (C-4), 171.40 (acetylic CO).

1-[(2-Acetoxyethoxy)methyl]-5-(4-hydroxybenzyl)-6-azauracil (5d): yield 77%. ^{1}H NMR($CDCl_3$): δ 2.01 (s, 3H, acetylic CH_3), 3.78 (s, 2H, benzylic CH_2), 3.79-4.20 (A_2B_2, 4H, OCH_2CH_2O), 5.31 (s, 2H, NCH_2O), 6.69 (d, 2H, aromatic CH, J=8.6Hz), 7.10 (d, 2H, aromatic CH, J=8.5Hz), 10.01 (br s, 1H, 3-NH). ^{13}C NMR($CDCl_3$): δ 21.29 (acetylic CH_3), 35.61 (benzylic C), 63.82 (C-4'), 68.56 (C-3'), 80.15 (C-1'), 116.02, 127.21, 130.90,155.52 (aromatic C), 146.91 (C-5), 149.45 (C-2), 156.70 (C-4), 171.82 (acetylic CO).

1-[(2-Acetoxyethoxy)methyl]-5-benzyl-6-azauracil (5e): yield 75%. ^{1}H NMR($CDCl_3$): δ 2.02 (s, 3H, acetylic CH_3), 3.89 (s, 2H, benzylic CH_2), 3.77-4.23 (A_2B_2, 4H, OCH_2CH_2O), 5.32 (s, 2H, NCH_2O), 7.20 (br s, 5H, aromatic CH), 10.29 (br s, 1H, 3-NH).

1-[(2-Hydroxyethoxy)methyl]-5-(4-methoxybenzyl)-6-azauracil (6a).

A solution of 5a (1.86g, 5.3mmol) in 50ml of 40% methylamine was heated to boiling. After 4 h, (monitored by TLC) the resulting

solution was evaporated and purified by column chromatography on silica gel (CH_2Cl_2-MeOH, 10:1), and crystallized from ethyl acetate to give 1.28g (79%) of 6a. mp: 103-105°C, ^1H NMR(DMSO-d_6): δ 3.46-3.58 (m, 4H, OCH_2CH_2O), 3.71 (s, 3H, OCH_3), 3.74 (s, 2H, benzylic CH_2), 4.66 (br s, 1H, 4'-OH), 5.18 (s, 2H, NCH_2O), 6.85 (d, 2H, aromatic CH, J=8.8Hz), 7.17 (d, 2H, aromatic CH, J=8.7Hz), 12.20 (br s, 1H, 3-NH), ^{13}C NMR(DMSO-d_6): δ 34.65 (benzylic C), 55.29 (OCH_3), 60.35 (C-4'), 71.31 (C-3'), 79.28 (C-1'), 114.08, 128.61, 130.19, 158.28 (aromactic C), 145.41 (C-5), 149.15 (C-2), 156.93 (C-4).
Anal. Cald. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.76. Found : C, 54.59; H, 5.60; N, 13.72.

The same reaction procedure was adopted to prepare 6b-c.
1-[(2-Hydroxyethoxy)methyl]-5-(4-chlorobenzyl)-6-azauracil (6b): yield 86%. mp: 121-123°C. ^1H NMR(DMSO-d_6): δ 3.43-3.58 (m, 4H, OCH_2CH_2O), 3.81 (s, 2H, benzylic CH_2), 4.65 (t, 1H, 4'-OH), 5.16 (s, 2H, NCH_2O), 7.28 (d, 2H, aromatic CH, J=8.8Hz), 7.35 (d, 2H, aromatic CH, J=8.7Hz), 12.23 (br s, 1H, 3-NH), ^{13}C NMR(DMSO-d_6): δ 34.82 (benzylic C), 60.33 (C-4'), 71.31 (C-3'), 79.29 (C-1'), 128.51, 131.07, 131.51, 135.88 (aromactic C), 144.80 (C-5), 149.14 (C-2), 156.94 (C-4).
Anal. Cald. for $C_{13}H_{14}ClN_3O4$: C, 50.08; H, 4.53; N, 13.48. Found : C, 49.85; H, 4.59; N, 13.31.

1-[(2-Hydroxyethoxy)methyl]-5-(4-methylbenzyl)-6-azauracil (6c): yield 82%. mp: 127-129°C. ^1H NMR(DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.47-3.58 (m, 4H, OCH_2CH_2O), 3.76 (s, 2H, benzylic CH_2), 4.65 (br s, 1H, 4'-OH), 5.17 (s, 2H, NCH_2O), 7.08 (d, 2H, aromatic CH, J=8.3Hz), 7.14 (d, 2H, aromatic CH, J=8.5Hz), 12.06 (br s, 1H, 3-NH), ^{13}C NMR(DMSO-d_6): δ 20.88 (CH_3), 35.09 (benzylic C), 60.34 (C-4'), 71.28 (C-3'), 79.28 (C-1'), 129.00, 129.20, 133.78, 135.82 (aromactic C), 145.27 (C-5), 149.23 (C-2), 157.01 (C-4).
Anal. Cald. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42. Found : C, 57.25; H, 5.89; N, 14.41.

1-[(2-Hydroxyethoxy)methyl]-5-(4-hydroxybenzyl)-6-azauracil (6d): yield 88%. mp: 103-105°C. ^1H NMR(DMSO-d_6): δ 3.42-3.59 (m, 4H,

OCH_2CH_2O), 3.68 (s, 2H, benzylic CH_2), 4.66 (t, 1H, 4'-OH), 5.17 (s, 2H, NCH_2O), 6.67 (d, 2H, aromatic CH, J=8.6Hz), 7.04 (d, 2H, aromatic CH, J=8.6Hz), 9.26 (br s, 1H, phenolic OH), 12.18 (br s, 1H, 3-NH), ^{13}C NMR(DMSO-d_6): δ 34.61 (benzylic C), 60.49 (C-4'), 71.53 (C-3'), 79.57 (C-1'), 116.05, 127.53, 130.87, 157.98 (aromactic C), 146.45 (C-5), 150.14 (C-2), 157.28 (C-4).
Anal. Cald. for $C_{13}H_{15}N_3O_5 \cdot H_2O$: C, 50.16; H, 5.50; N, 13.50. Found : C, 50.73; H, 5.26; N, 13.58.

1-[(2-Hydroxyethoxy)methyl]-5-benzyl-6-azauracil (6e): yield 78%. ^1H NMR(DMSO-d_6): δ 3.68 (s, 4H, OCH_2CH_2O), 3.84 (s, 2H, benzylic CH_2), 4.53 (br s, 1H, 4'-OH), 5.26 (s, 2H, NCH_2O), 7.17 (s, 5H, aromatic CH), 12.26 (br s, 1H, 3-NH), ^{13}C NMR(DMSO-d_6): δ 35.53 (benzylic C), 61.06 (C-4'), 71.03 (C-3'), 79.46 (C-1'), 126.64, 128.24, 128.98, 135.59 (aromactic C), 145.78 (C-5), 149.04 (C-2), 156.27 (C-4).
Anal. Cald. for $C_{13}H_{15}N_3O4$: C, 56.31; H, 5.45; N, 15.15. Found : C, 56.23; H, 5.40; N, 15.21.

1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-5-(4-methoxybenzyl)-6-azauracil (7a).

5-(4-Methoxybenzyl)-6-azauracil 4a (1.50g, 6.4mmol) was silylated with hexamethyldisilazane (HMDS, 35ml) and a small amount of chlorotrimethylsilane. The silylation intermidate was dissolved in 1,2-dichloroethane (15ml) and to which was added (1,3-dibenzyloxy-2-propoxy)methyl bromide (2.06g, 6.2mmol) in 1,2-dichloroethane (15ml). The solution was stirred at room temperature for 18 h, and the resulting solution was evaporated and chromatographied on silica gel (CH_2Cl_2-MeOH, 50:1) to give 1.79g (54%) of 7a as a yellow syrup. ^1H NMR($CDCl_3$): δ 3.48-3.61 (m, 4H, 4'-H), 3.75 (s, 3H, OCH_3), 3.78 (s, 2H, benzylic CH_2), 4.45 (s, 4H, benzyloxy CH_2), 5.43 (s, 2H, NCH_2O), 6.81 (d, 2H, aromatic CH, J=8.7Hz), 7.22-7.32 (m, 12H, all aromatic CH), 9.13 (brs, 1H, 3-NH).

The same procedure was used to convert each of the compounds 6b-e to the respective 7b-e.

1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-5-(4-chlorobenzyl)-6-azauracil (7b): yield 53%. ^{1}H NMR($CDCl_3$): δ 3.51-3.62 (m, 4H, 4'-H), 3.81 (s, 2H, benzylic CH_2), 4.16 (m, 1H, 3'-H), 4.46 (s, 4H, benzyloxy CH_2), 5.44 (s, 2H, NCH_2O), 7.23-7.34 (m, 14H, all aromatic CH), 9.52 (brs, 1H, 3-NH).

1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-5-(4-methylenzyl)-6-azauracil (7c): yield 54%. ^{1}H NMR($CDCl_3$): δ 2.28 (s, 3H, CH_3), 3.47-3.60 (m, 4H, 4'-H), 3.80 (s, 2H, benzylic CH_2), 4.14 (m, 1H, 3'-H), 4.44 (s, 4H, benzyloxy CH_2), 5.42 (s, 2H, NCH_2O), 7.05-7.32 (m, 14H, all aromatic CH), 9.00 (brs, 1H, 3-NH).

1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-5-(4-hydroxybenzyl)-6-azauracil (7d): yield 58%. ^{1}H NMR($CDCl_3$): δ 3.49 (d, 4H, 4'-H), 3.66 (s, 2H, benzylic CH_2), 4.12 (m, 1H, 3'-H), 4.42 (s, 4H, benzyloxy CH_2), 5.37 (s, 2H, NCH_2O), 6.65 (d, 2H, aromatic CH, J=8.6Hz), 6.76 (br s, 1H, phenolic OH), 7.07 (d, 2H, aromatic CH, J=8.4Hz), 7.18-7.29 (m, 10H, aromatic CH), 9.95 (brs, 1H, 3-NH).

1-[(1,3-Dibenzyloxy-2-propoxy)methyl]-5-benzyl-6-azauracil (7e): yield 77%. ^{1}H NMR($CDCl_3$): δ 3.50 (d, 4H, 4'-H, J=5.4Hz), 3.82 (s, 2H, benzylic CH_2), 4.14 (m, 1H, 3'-H, J=5.5Hz), 4.43 (s, 4H, benzyloxy CH_2), 5.41 (s, 2H, NCH_2O), 7.24 (br s, 15H, aromatic CH), 9.65 (brs, 1H, 3-NH).

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-(4-methoxybenzyl)-6-azauracil (8a).

Compound 7a (1.48g, 2.8mmol), palladium hydroxide on carbon (600mg), cyclohexene (5ml) and ethanol (35ml) were refluxed for 4 h. The resulting solution was filtered and the filtrate evaporated to give a residual oil which was purified with silica gel column chromatogrophy (CH_2Cl_2-MeOH, 15:1) to give 0.64g (78%) of 8a as a colorless oil. ^{1}H NMR(DMSO-d_6): δ 3.27-3.49 (m, 4H, 4'-H), 3.63 (m, 1H, 3'-H), 3.71 (s, 1H, OCH_3), 3.74 (s, 2H, benzylic CH_2), 4.59 (t, 2H, 4'-OH), 5.26 (s, 2H, NCH_2O), 6.84 (d, 2H, aromatic CH, J=8.8Hz), 7.18 (d, 2H, aromatic CH, J=8.8Hz), 12.16 (br s, 1H, 3-NH). ^{13}C NMR(DMSO-d_6): δ 34.70 (benzylic C), 55.29 (OCH_3), 61.32 (C-4'), 78.79 (C-1'),

81.25 (C-3'), 114.06, 128.65, 130.19, 158.26 (aromatic C), 145.18 (C-5), 149.14 (C-2), 156.97 (C-4).
Anal. Cald. for $C_{15}H_{19}N_3O_6 \cdot 1.5H_2O$: C, 49.45; H, 6.08; N, 11.53. Found : C, 49.77; H, 6.07; N, 11.31.

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-(4-chlorobenzyl)-6-azauracil (8b).

Compound 7b was debenzylated with palladium hydroxide by same procedure as 8a. The residual solid was crystallized with MeOH to give 8b (86%). mp: 121-123°C. ^{1}H NMR(DMSO-d_6): δ 3.28-3.47 (m, 4H, 4'-H), 3.64 (m, 1H, 3'-H), 3.79 (s, 2H, benzylic CH_2), 4.60 (br s, 2H, 4'-OH), 5.26 (s, 2H, NCH_2O), 7.24-7.37 (m, 4H, aromatic CH), 12.12 (br s, 1H, 3-NH). ^{13}C NMR(DMSO-d_6): δ 34.87 (benzylic C), 61.31 (C-4'),, 78.79 (C-1'), 81.29 (C-3'), 128.50, 131.06, 131.48, 135.91 (aromatic C), 144.54 (C-5), 149.13 (C-2), 156.99 (C-4).
Anal. Cald. for $C_{14}H_{16}ClN_3O_5$: C, 49.20; H, 4.72; N, 12.30. Found : C, 49.12; H, 4.75; N, 12.24.

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-(4-methylbenzyl)-6-azauracil (8c).

Compound 7c was debenzylated with palladium hydroxide by same procedure as 8a, The residual solid was crystallized with acetone-methanol to give 8c (81%). mp: 148-150°C. ^{1}H NMR(DMSO-d_6): δ 2.25 (s, 3H, CH_3), 3.27-3.49 (m, 4H, 4'-H), 3.64 (m, 1H, 3'-H), 3.76 (s, 2H, benzylic CH_2), 4.60 (t, 2H, 4'-OH), 5.26 (s, 2H, NCH_2O), 7.08 (d, 2H, aromatic CH, J=8.1Hz), 7.15 (d, 2H, aromatic CH, J=8.2Hz), 12.18 (br s, 1H, 3-NH). ^{13}C NMR(DMSO-d_6): δ 20.89 (CH_3), 35.14 (benzylic C), 61.28 (C-4'), 78.79 (C-1'), 81.23 (C-3'), 129.00, 129.19, 133.77, 135.79 (aromatic C), 145.05 (C-5), 149.16 (C-2), 156.97 (C-4).
Anal. Cald. for $C_{15}H_{19}N_3O_5$: C, 56.07; H, 5.96; N, 13.08. Found : C, 55.80; H, 5.99; N, 12.99.

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-(4-hydroxybenzyl)-6-azauracil (8d).

Compound 7d was debenzylated with palladium hydroxide by same procedure as 8a. The residual oil was purified with silica gel

column chromatogrophy (CH_2Cl_2-MeOH=10:1) to give 8d (89%). ^1H NMR (DMSO-d_6): δ 3.32-3.51 (m, 4H, 4'-H), 3.68 (m, 1H, 3'-H), 3.71 (s, 2H, benzylic CH_2), 4.61 (t, 2H, 4'-OH), 5.27 (s, 2H, NCH_2O), 6.71 (d, 2H, aromatic CH, J=8.6Hz), 7.10 (d, 2H, aromatic CH, J=8.6Hz), 9.29 (br s, 1H, phenolic OH), 12.25 (br s, 1H, 3-NH). ^{13}C NMR(DMSO-d_6): δ 34.65 (benzylic C), 61.45 (C-4'), 79.09 (C-1'), 81.52 (C-3'), 116.03, 127.56, 130.86, 158.05 (aromatic C), 146.22 (C-5), 150.14 (C-2), 157.24 (C-4).

Anal. Cald. for $C_{14}H_{17}N_3O_6 \cdot H_2O$: C, 49.26; H, 5.61; N, 12.31. Found : C, 48.76; H, 5.72; N, 12.04.

1-[(1,3-Dihydroxy-2-propoxy)methyl]-5-benzyl-6-azauracil (8e).

Compound 7e was debenzylated with palladium hydroxide by same procedure as 8a. The residual solid was crystallized with ethanol to give 8e (81%). mp: 106-107°C. ^1H NMR (DMSO-d_6): δ 3.40-3.70 (complex, 5H, 3'- and 4'-H), 3.82 (s, 2H, benzylic CH_2), 4.58 (br s, 2H, 4'-OH), 5.28 (s, 2H, NCH_2O), 7.27 (s, 5H, aromatic CH), 12.20 (br s, 1H, 3-NH). ^{13}C NMR(DMSO-d_6): δ 35.48 (benzylic C), 61.26 (C-4'), 78.76 (C-1'), 81.20 (C-3'), 126.74, 128.58, 129.09, 136.67 (aromatic C), 144.87 (C-5), 149.12 (C-2), 156.98 (C-4).

Anal. Cald. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found : C, 54.60; H, 5.62; N, 13.66.

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