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# Synthesis and antimicrobial evaluation of 6-azauracil non-nucleosides

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**Abstract** The present study describes synthesis and antimicrobial evaluation of a series of novel 6-azauracil non-nucleosides. Reaction of silylated 6-azauracils with the appropriate chloroethers gave the corresponding non-nucleosides. 1-(Allyloxymethy)-6-azauracils and non-nucleosides bearing indanyl, cyclohexenyl, and cyclohexyl moieties were obtained *via* silylation of 6-azauracils followed by treatment with the appropriate acetals. Selected compounds were tested for their *in vitro* antimicrobial activity against a panel of standard strains of *Gram*-positive and *Gram*-negative bacteria and the yeast-like pathogenic fungus *Candida albicans*. Four compounds showed marked inhibitory activity particularly against the tested *Gram*-positive bacteria.

**Keywords** 6-Azauracils; 6-Azathymines; 1,2,4-Triazine-3,5-diones; Non-nucleosides; Antimicrobial activity.

## Introduction

6-Azauracils (1,2,4-triazine-3,5(2*H*,4*H*)-diones) represent an important class of heterocyclic compounds. In recent years, much effort has been done on the synthesis and biological evaluation of 6-azauracil derivatives due to their possible applications. Many 6-azauracils have been demonstrated to exhibit herbicidal [1, 2], antiviral [3–6], antimicrobial [7–11], and anti-inflammatory activities [12]. As well as antimalarial [13], anticancer [14, 15], and antiulcer [16] activities have been reported.

On the other hand, the chemistry and diverse applications of non-nucleoside derivatives have received much attention due to their important biological activity. Several non-nucleosides have been reported as reverse transcriptase inhibitors of human immunodeficiency virus type-1 (HIV-1), the causative agent of the acquired immunodeficiency syndrome (AIDS) [17–20]. Non-nucleoside reverse transcriptase inhibitors, in contrast to other reverse transcriptase inhibitors, are highly specific as their binding site is a hydrophobic pocket located approximately 10 Å from the polymerase active site. They bind allosterically forcing the reverse transcriptase-subunit into an inactive conformation [18]. In the present study, and as a part of interest in the chemistry of non-nucleosides [21–30], the synthesis and antimicrobial evaluation of some novel 6-azauracil non-nucleosides have been described.

## Results and discussions

5-Substituted 6-azauracil derivatives **4a**–**4d** were prepared *via* the semicarbazones **3a**–**3d**, by the reaction of semicarbazide hydrochloride (**2**) with the appropriate $\alpha$-keto acids **1a**–**1d**, according to literature procedure [31]. Cyclization of the semicarbazones **3a**–**3d** was achieved by treatment with

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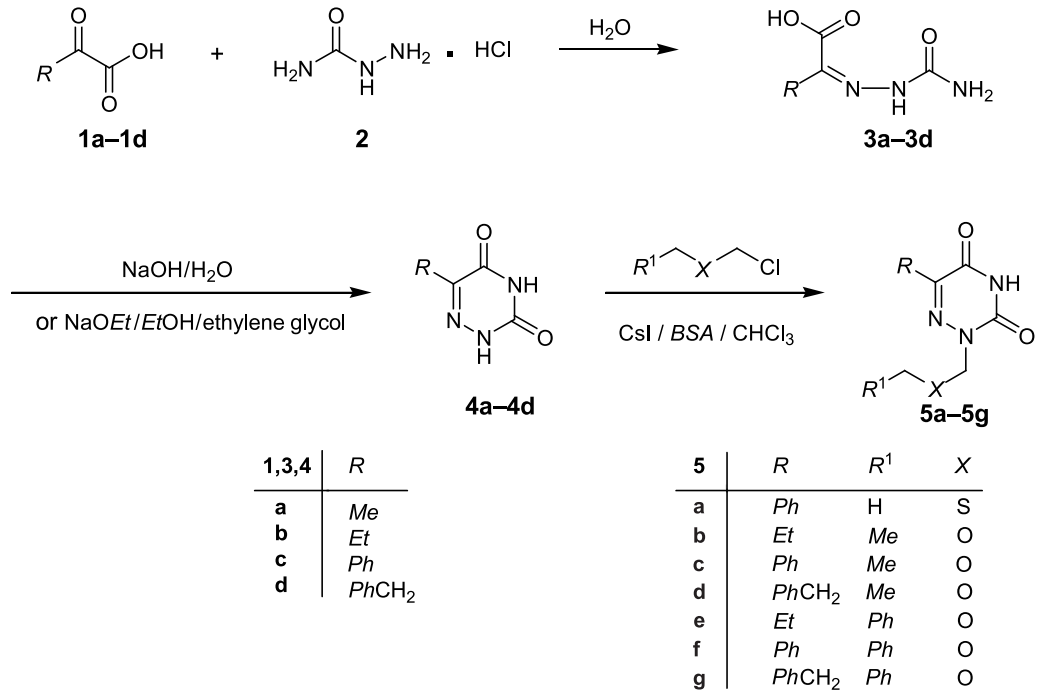



| 1,3,4 | R |
|---|---|
| a | *Me* |
| b | *Et* |
| c | *Ph* |
| d | *Ph*$CH_2$ |

| 5 | R | $R^1$ | X |
|---|---|---|---|
| a | *Ph* | H | S |
| b | *Et* | *Me* | O |
| c | *Ph* | *Me* | O |
| d | *Ph*$CH_2$ | *Me* | O |
| e | *Et* | *Ph* | O |
| f | *Ph* | *Ph* | O |
| g | *Ph*$CH_2$ | *Ph* | O |

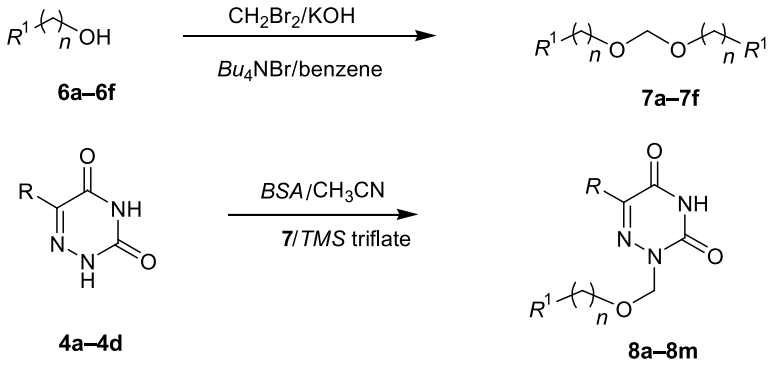
**Scheme 1**

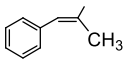
aqueous sodium hydroxide to give the corresponding 5-substituted 6-azauracils **4a**–**4d** in good yields except in the case of **4b**, for which the yield was poor. Sodium ethoxide in ethanol and ethylene glycol was used instead of aqueous sodium hydroxide to afford **4b** [5]. 6-Azauracils **4b**–**4d** were silylated with *N*,*O*-bis(trimethylsilyl)acetamide (*BSA*) in anhydrous chloroform followed by alkylation with chloromethyl methyl sulfide, chloromethyl methyl ether, and/or benzyl chloromethyl ether in the presence of cesium iodide to give the corresponding non-nucleosides **5a**–**5g** in 51–71% yields (Scheme 1).

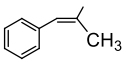
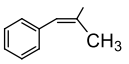
Bis(allyloxy)methane (**7a**), bis(2-methylallyloxy)-methane (**7b**), bis[(*E*)-2-methyl-3-phenylallyloxy]-methane (**7c**), bis(indan-2-yloxy)methane (**7d**), bis(3-cyclohexen-1-ylmethoxy)methane (**7e**), and bis(2-cyclohexylethoxy)methane (**7f**) were prepared from the corresponding alcohols; allyl alcohol (**6a**), 2-methylallyl alcohol (**6b**), (*E*)-2-methyl-3-phenylallyl alcohol (**6c**), 2-indanol (**6d**), 3-cyclohexen-1-methanol (**6e**), and 2-cyclohexylethanol (**6f**) were reacted with dibromomethane using potassium hydroxide in anhydrous benzene in the presence of tetrabutylammonium bromide according to the method of *Nazaretyan et al*. [32].

Silylation of **4a**–**4d** with *BSA* in anhydrous acetonitrile followed by treatment with the acetals **7a**, **7b**, or **7**c under the *Vorbrüggen* conditions [33] using trimethylsilyl trifluoromethanesulfonate (*TMS* triflate) as a *Lewis* acid catalyst afforded 1-allyloxymethyl-6-azauracil (**8a**), 1-(2-methylallyl-oxymethyl)-6-azauracils **8b**–**8e**, and 1-[(*E*)-2-methyl-3-phenylallyloxymethyl]-6-azauracils **8f**, **8g** in 67%, 54–70%, and 62, 68% yields. Synthesis of non-nucleosides bearing indanyl, cyclohexenyl, and cyclohexyl moieties (**8h**–**8m**) was investigated. Compounds **4b** and **4c** were silylated with *BSA* in anhydrous acetonitrile and treated with **7d** in the presence of *TMS* triflate to give 5-ethyl-1-(indan-2-yloxymethyl)-6-azauracil (**8h**) and 1-(indan-2-yloxy-methyl)-5-phenyl-6-azauracil (**8i**) in 53 and 61% yields. Silylation of 5-phenyl-6-azauracil (**4c**) followed by reaction with **7e** in the presence of *TMS* triflate afforded 1-(3-cyclohexen-ylmethoxymethyl)-5-phenyl-6-azauracil (**8j**) in 64% yield. 1-(2-Cyclohexylethoxymethyl)-6-azauracils (**8k**–**8m**) were obtained in 23–54% yields, by treatment of **4a**–**4c** with the acetal **7f** under the same reaction conditions (Scheme 2).

The acetals **7a**–**7e** were prepared previously [21, 22, 24]. N-1 Alkylation was proved by comparison




| 6, 7 | $R^1$ | n |
|---|---|---|
| a | $H_2C{=}CH-$ | 1 |
| b | $H_2C{=}C(CH_3)-$ | 1 |
| c |  | 1 |
| d |  | 0 |
| e |  | 1 |
| f |  | 2 |

| 8 | R | $R^1$ | n |
|---|---|---|---|
| a | *Ph* | $H_2C{=}CH-$ | 1 |
| b | *Me* | $H_2C{=}C(CH_3)-$ | 1 |
| c | *Et* | $H_2C{=}C(CH_3)-$ | 1 |
| d | *Ph* | $H_2C{=}C(CH_3)-$ | 1 |
| e | $PhCH_2$ | $H_2C{=}C(CH_3)-$ | 1 |
| f | *Me* |  | 1 |
| g | *Ph* |  | 1 |
| h | *Et* |  | 0 |
| i | *Ph* |  | 0 |
| j | *Ph* |  | 1 |
| k | *Me* |  | 2 |
| l | *Et* |  | 2 |
| m | *Ph* |  | 2 |

**Scheme 2**

with similar NMR data [34, 35]. The *N*-3 regioisomer was not observed.

The newly synthesized non-nucleosides **5a–5g**, **8a**, **8d**, **8g**–**8j**, and **8m** were tested for their *in vitro* antimicrobial activity against a panel of standard strains of *Gram*-positive bacteria (*Staphylococcus aureus* IFO 3060 and *Bacillus subtilis* IFO 3007), *Gram*-negative bacteria (*Escherichia coli* IFO 3301 and *Pseudomonas aeuroginosa* IFO 3448), and the yeast-like pathogenic fungus *Candida albicans* IFO 0583 using the agar disc-diffusion method [36]. The results of the preliminary antimicrobial testing of **5a–5g**, **8a**, **8d**, **8g**–**8j**, and **8m** (200 $\mu$g/disc), the antibacterial antibiotic Ampicillin trihydrate (100 $\mu$g/disc), and the antifungal drug Clotrimazole (100 $\mu$g/disc) are shown in Table 1. In general, the best antibacterial activity was displayed by **5a** which showed potent inhibitory activity against the tested *Gram*-positive bacteria and medium activity against the tested *Gram*-negative bacteria. Meanwhile, **5b**, **5e**, and **8h** were active against the tested *Gram*-positive bacteria and almost inactive against the tested *Gram*-negative bacteria. None of the tested compounds was found to be

**Table 1** Antimicrobial activity of **5a–5g**, **8a**, **8d**, **8g–8j** and **8m** (200 $\mu$g/8 mm disc), the broad spectrum antibacterial drug Ampicillin (100 $\mu$g/8 mm disc) and the antifungal drug Clotrimazole (100 $\mu$g/8 mm disc) against *Staphylococcus aureus* IFO 3060 (*SA*), *Bacillus subtilis* IFO 3007 (*BS*), *Escherichia coli* IFO 3301 (*EC*), *Pseudomonas aeuroginosa* IFO 3448 (*PA*), and *Candida albicans* IFO 0583 (*CA*)

| Comp. no. | Diameter of growth inhibition zone mm* | | | | |
|---|---|---|---|---|---|
| | *SA* | *BS* | *EC* | *PA* | *CA* |
| **5a** | 18 | 18 | 15 | 14 | 13 |
| **5b** | 18 | 16 | 11 | – | – |
| **5c** | 14 | 15 | – | – | – |
| **5d** | 15 | 14 | – | – | – |
| **5e** | 18 | 24 | 12 | – | – |
| **5f** | 12 | 10 | – | – | – |
| **5g** | 10 | 10 | – | – | – |
| **8a** | 14 | 10 | – | – | – |
| **8d** | 12 | 10 | – | – | – |
| **8g** | 10 | – | – | – | – |
| **8h** | 17 | 19 | 10 | – | – |
| **8i** | – | 10 | – | – | – |
| **8j** | – | 13 | – | – | – |
| **8m** | – | 10 | – | – | – |
| Ampicillin | 19 | 18 | 16 | 15 | NT |
| Clotrimazole | NT | NT | NT | NT | 21 |

* –:Inactive (inhibition zone <10 mm); NT: Not tested

superior to Clotrimazole against *Candida albicans*, only **5a** produced weak activity.

## Experimental

NMR spectra were recorded on a Bruker AC 500 Ultra Shield NMR spectrometer at 500 MHz for $^1$H and 125 MHz for $^{13}$C with *TMS* as an internal standard. Chemical shifts are reported in ppm ($\delta$), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Electron impact mass spectra were recorded on a Jeol JMS-AX 500 mass spectrometer, melting points were determined on a Gallenkamp melting point apparatus. Elemental analysis were alone with a their results agreed favourably with calculated values. The progress of reactions was monitored by TLC (DC-alufolio 60 $F_{254}$) from Merck. For column chromatography Merck silica gel (0.040–0.063 mm) was used. The bacterial strains and *Candida albicans* fungus were obtained from the Institute of fermentation of Osaka (IFO), Osaka, Japan. The reference drugs Ampicillin trihydrate (CAS 7177-48-2) and Clotrimazole (CAS 23593-75-1) were obtained from Sigma-Aldrich Chemie GmbH, Taufkirchen, Germany.

*General procedure for preparation of 6-azauracil non-nucleosides **5a–5g***

*N*,*O*-Bis(trimethylsilyl)acetamide (*BSA*) (0.87 cm$^3$, 3.5 mmol) was added to a suspension of 1.0 mmol 6-azauracil **4b–4d** in anhydrous 20 cm$^3$ $CHCl_3$ and the mixture was stirred at room temperature under nitrogen. After a clear solution was obtained (20–30 min), chloromethyl methyl sulphide, chloromethyl ethyl ether, or benzyl chloromethyl ether (1.5 mmol) was added, followed by addition of (0.26 g, CsI 1 mmol). The reaction mixture was stirred at room temperature under nitrogen for 3–4 h. Sat aq $NaHCO_3$ (20 cm$^3$) was added and the mixture was extracted with $3 \times 50$ cm$^3$ $CH_2Cl_2$. The organic phase was collected, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel column using $CHCl_3$ to give **5a–5g**.

*1-Methylthiomethyl-5-phenyl-6-azauracil* (**5a**, $C_{11}H_{11}N_3O_2S$)
White solid; yield 0.152 g (61%); mp 184–185°C; $^1$H NMR (*DMSO*-$d_6$, 500 MHz): $\delta = 2.27$ (s, 3H, $CH_3$), 5.06 (s, 2H, $CH_2$), 7.46–7.48, 7.89–7.91 ($2 \times$ m, 5H, $H_{arom}$), 12.38 (s, 1H, NH) ppm; $^{13}$C NMR (DMSO-$d_6$, 125 MHz): $\delta = 15.40$ ($CH_3$), 54.15 ($CH_2$), 128.57, 128.60, 130.14, 132.42 ($C_{arom}$), 141.78 (C-5), 148.46 (C-2), 156.92 (C-4) ppm; MS (EI): $m/z$ (%) = 249 ($M^+$, 51), 243 (9), 228 (17), 208 (19), 203 (56), 191 (13), 165 (12), 147 (23), 131 (68), 104 (42), 91 (100).

*5-Ethyl-1-ethoxymethyl-6-azauracil* (**5b**, $C_8H_{13}N_3O_3$)
White solid; yield 0.137 g (69%); mp 76–77°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.21$ (t, $J = 7.5$ Hz, 3H, $CH_3$), 124 (t, $J = 7.0$ Hz, 3H, $CH_3$), 2.65 (q, $J = 7.0$ Hz, 2H, $CH_2$), 3.69 (q, $J = 7.5$ Hz, 2H, $CH_2$), 5.33 (s, 2H, $CH_2$), 9.93 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 10.36$ ($CH_3$), 15.00 ($CH_3$), 23.23 ($CH_2$), 65.70 ($CH_2$), 79.32 ($CH_2$), 148.04 (C-5), 149.09 (C-2), 156.38 (C-4) ppm; MS (EI): $m/z$ (%) = 199 ($M^+$, 36), 170 (14), 155 (83), 142 (27), 127 (8), 112 (34), 100 (82), 83 (86) 58 (100).

*1-Ethoxymethyl-5-phenyl-6-azauracil* (**5c**, $C_{12}H_{13}N_3O_3$)
White solid; yield 0.175 g (71%); mp 122–123°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.26$ (t, $J = 7.0$ Hz, 3H, $CH_3$), 3.76 (q, $J = 7.0$ Hz, 2H, $CH_2$), 5.45 (s, 2H, $CH_2$), 7.45–7.48, 8.03–8.05 ($2 \times$ m, 5H, $H_{arom}$), 10.08 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 15.03$ ($CH_3$), 65.89 ($CH_2$), 79.81 ($CH_2$), 128.35, 128.40, 130.42, 131.13 ($C_{arom}$), 142.34 (C-5), 148.78 (C-2), 155.97 (C-4) ppm; MS (EI): $m/z$ (%) = 247 ($M^+$, 57), 203 (29), 190 (10), 175 (6), 131 (32), 118 (34), 104 (93), 89 (51), 58 (100).

*5-Benzyl-1-ethoxymethyl-6-azauracil* (**5d**, $C_{13}H_{15}N_3O_3$)
White solid; yield 0.154 g (59%); mp 96–97°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.23$ (t, $J = 7.0$ Hz, 3H, $CH_3$), 3.67 (q, $J = 7.0$ Hz, 2H, $CH_2$), 3.95 (s, 2H, $CH_2$), 5.32 (s, 2H, $CH_2$), 7.25–7.36 (m, 5H, $H_{arom}$), 9.71 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 15.00$ ($CH_3$), 35.92 ($CH_2$), 65.70 ($CH_2$), 79.35 ($CH_2$), 127.02, 128.59, 129.25, 135.75 ($C_{arom}$), 145.92 (C-5), 148.89 (C-2), 156.04 (C-4) ppm; MS (EI): $m/z$ (%) = 261 ($M^+$, 39), 232 (6), 217 (25), 203 (11), 184 (9), 171 (22), 118 (16), 91 (100).

*1-Benzyloxymethyl-5-ethyl-6-azauracil* (**5e**, $C_{13}H_{15}N_3O_3$)
White solid; yield 0.151 g (58%); mp 86–88°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.22$ (t, $J = 7.0$ Hz, 3H, $CH_3$), 2.63 (q, $J = 7.0$ Hz, 2H, $CH_2$), 4.75 (s, 2H, $CH_2$), 5.42 (s, 2H,

$CH_2$), 7.29–7.36 (m, 5H, $H_{arom}$), 9.81 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 10.32$ ($CH_3$), 23.22 ($CH_2$), 72.02 ($CH_2$), 79.03 ($CH_2$), 127.69, 127.89, 128.37, 137.38 ($C_{arom}$), 148.04 (C-5), 149.07 (C-2), 156.21 (C-4) ppm; MS (EI): $m/z$ (%) = 261 ($M^+$, 11), 244 (3), 232 (6), 181 (4), 155 (47), 147 (16), 107 (31), 91 (100).

*1-Benzyloxymethyl-5-phenyl-6-azauracil* (**5f**, $C_{17}H_{15}N_3O_3$)
White solid; yield 0.195 g (63%); mp 124–125°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 4.80$ (s, 2H, $CH_2$), 5.53 (s, 2H, $CH_2$), 7.28–8.05 (m, 10H, $H_{arom}$), 9.92 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 72.20$ ($CH_2$), 79.51 ($CH_2$), 127.02, 127.76, 127.96, 128.36, 128.41, 130.45, 131.12, 137.27 ($C_{arom}$), 142.40 (C-5), 148.71 (C-2), 155.74 (C-4) ppm; MS (EI): $m/z$ (%) = 309 ($M^+$, 11), 203 (78), 176 (16), 160 (6), 147 (53), 131 (24), 118 (12), 104 (72), 91 (100).

*5-Benzyl-1-benzyloxymethyl-6-azauracil* (**5g**, $C_{18}H_{17}N_3O_3$)
White solid; yield 0.165 g (51%); mp 73–74°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 3.94$ (s, 2H, $CH_2$), 4.71 (s, 2H, $CH_2$), 5.40 (s, 2H, $CH_2$), 7.30–7.38 (m, 10H, $H_{arom}$), 9.69 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 35.89$ ($CH_2$), 71.99 ($CH_2$), 78.97 ($CH_2$), 127.07, 127.74, 127.90, 128.37, 128.63, 129.35, 135.73, 137.23 ($C_{arom}$), 146.01 (C-5), 146.89 (C-2), 155.94 (C-4) ppm; MS (EI): $m/z$ (%) = 323 ($M^+$, 13), 232 (10), 217 (65), 204 (7), 161 (43), 131 (19), 118 (7), 91 (100).

*Bis(2-cyclohexylethoxy)methane* (**7f**, $C_{17}H_{32}O_2$)
2-Cyclohexylethanol (**6f**, 12.8 g, 0.1 mol), 8.79 g (dibromomethane 0.0505 mol), and 1.74 g (tetrabutylammonium bromide 0.00535 mol) were added to 5.66 g (potassium hydroxide 0.101 mol) in 30 $cm^3$ anhydrous benzene, and the suspension was heated under reflux for 5 h. After cooling, (50 $cm^3$) $H_2O$ were added and the resulting solution was extracted with $3 \times 50$ $cm^3$ ether. The ether phase was dried with anhydrous $MgSO_4$ and evaporated under reduced pressure to afford **7f** as a colorless oil in 55% (7.4 g) yield. As determined from NMR, the desired **7f** was contaminated with the starting material **6f** in a 5:2 ratio. The product was used for further synthesis without purification. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 0.90$–1.69 (m, 26H, $H_{hexyl}$, $2 \times CH_2$), 3.59 (t, $J = 6.5$ Hz, 4H, $2 \times CH_2$), 4.66 (s, 2H, $CH_2$) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 26.17$, 26.59, 33.38, 34.58 ($C_{hexyl}$), 37.17 ($CH_2$), 65.70 ($CH_2$), 95.23 ($CH_2$) ppm.

*General procedure for preparation of 1-allyloxymethyl-6-azauracils **8a–8g***
Compound **4a–4d** (1 mmol) was stirred in 15 $cm^3$ anhydrous $CH_3CN$ under nitrogen and 0.87 $cm^3$ (*BSA* 3.5 mmol) were added. After a clear solution was obtained (10 min), the reaction mixture was cooled to −50°C and 0.18 $cm^3$ (*TMS* triflate 1 mmol) were added followed by dropwise addition of 2 mmol **7a–7c** appropriate acetal. The mixture was stirred at room temperature for 4 h. The reaction was quenched with 5 $cm^3$ sat aq $NaHCO_3$ solution and evaporated under reduced pressure. The residue was extracted with $3 \times 50$ $cm^3$ ether, the combined organic fractions were dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on silica gel column with $CHCl_3$ to afford the desired non-nucleosides **8a–8g**.

*1-Allyloxymethyl-5-phenyl-6-azauracil* (**8a**, $C_{13}H_{13}N_3O_3$)
White solid; yield 0.174 g (67%); mp 101–102°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 4.26$ (d, $J = 5.5$ Hz, 2H, $CH_2$), 5.24 (d, $J = 10.5$ Hz, 1H, $CH_{(Z)}$=), 5.35 (d, $J = 17.0$ Hz, 1H, $CH_{(E)}$=), 5.48 (s, 2H, $CH_2$), 5.90–5.98 (m, 1H, =CH–), 7.28–7.47, 8.03–8.05 ($2 \times$ m, 5H, $H_{arom}$), 10.14 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 71.04$ ($CH_2$), 79.26 ($CH_2$), 117.98 ($CH_2$=), 128.38, 128.40, 130.47, 131.08 ($C_{arom}$), 133.38 (=CH–), 142.44 (C-5), 148.89 (C-2), 155.99 (C-4) ppm; MS (EI): $m/z$ (%) = 259 ($M^+$, 14), 228 (5), 202 (28), 190 (21), 175 (4), 160 (6), 131 (43), 115 (17), 104 (100).

*5-Methyl-1-(2-methylallyloxymethyl)-6-azauracil*
(**8b**, $C_9H_{13}N_3O_3$)
White solid; yield 0.118 g (56%); mp 71–72°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.74$ (s, 3H, $CH_3$), 2.26 (s, 3H, $CH_3$), 4.08 (s, 2H, $CH_2$), 4.91, 5.00 ($2 \times$ s, 2H, $CH_2$=), 5.32 (s, 2H, $CH_2$), 10.23 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 16.17$ ($CH_3$), 19.32 ($CH_3$), 73.82 ($CH_2$), 78.70 ($CH_2$), 112.80 ($CH_2$=), 141.20 (C-5), 144.43 (=C(*Me*)–), 149.31 (C-2), 156.76 (C-4) ppm; MS (EI): $m/z$ (%) = 211 ($M^+$, 15), 196 (8), 141 (9), 127 (5), 112 (6), 85 (11), 70 (29), 42 (100).

*5-Ethyl-1-(2-methylallyloxymethyl)-6-azauracil*
(**8c**, $C_{10}H_{15}N_3O_3$)
Colorless viscous oil; yield 0.122 g (54%); $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.20$ (t, $J = 7.5$ Hz, 3H, $CH_3$), 1.74 (s, 3H, $CH_3$), 2.65 (q, $J = 7.5$ Hz, 2H, $CH_2$), 4.09 (s, 2H, $CH_2$), 4.92, 5.01 ($2 \times$ s, 2H, $CH_2$=), 5.34 (s, 2H, $CH_2$), 10.17 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 10.31$ ($CH_3$), 19.32 ($CH_3$), 23.20 ($CH_2$), 73.86 ($CH_2$), 78.74 ($CH_2$), 112.79 ($CH_2$=), 141.27 (C-5), 148.06 (=C(*Me*)–), 149.22 (C-2), 156.46 (C-4) ppm; MS (EI): $m/z$ (%) = 225 ($M^+$, 24), 196 (5), 155 (13), 154 (61), 141 (16), 112 (4), 85 (7), 70 (19), 56 (100).

*1-(2-Methylallyloxymethyl)-5-phenyl-6-azauracil*
(**8d**, $C_{14}H_{15}N_3O_3$)
White solid; yield 0.19 g (70%); mp 125–126°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.77$ (s, 3H, $CH_3$), 4.17 (s, 2H, $CH_2$), 4.96, 5.05 ($2 \times$ s, 2H, $CH_2$=), 5.47 (s, 2H, $CH_2$), 7.45–7.50, 8.04–8.06 ($2 \times$ m, 5H, $H_{arom}$), 10.13 (s, 1H, NH) ppm; $^{13}C$ NMR ($CDCl_3$, 125 MHz): $\delta = 19.38$ ($CH_3$), 74.03 ($CH_2$), 79.25 ($CH_2$), 113.00 ($CH_2$=), 128.38, 128.39, 130.44, 131.12 ($C_{arom}$), 141.21 (C-5), 142.37 (=C(*Me*)–), 148.85 (C-2), 155.98 (C-4) ppm; MS (EI): $m/z$ (%) = 273 ($M^+$, 14), 245 (4), 202 (73), 190 (16), 171 (3), 131 (58), 111 (13), 104 (75), 53 (100).

*5-Benzyl-1-(2-methylallyloxymethyl)-6-azauracil*
(**8e**, $C_{15}H_{17}N_3O_3$)
White solid; yield 0.158 g (55%); mp 76–77°C; $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta = 1.73$ (s, 3H, $CH_3$), 3.95 (s, 2H,

$CH_2$), 4.07 (s, 2H, $CH_2$), 4.91, 4.97 (2 × s, 2H, $CH_2$=), 5.33 (s, 2H, $CH_2$), 7.25–7.36 (m, 5H, $H_{arom}$), 9.48 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 19.32$ ($CH_3$), 35.90 ($CH_2$), 73.85 ($CH_2$), 78.80 ($CH_2$), 112.82 ($CH_2$=), 127.05, 128.61, 129.27, 135.69 ($C_{arom}$), 141.17 (C-5), 145.86 (=C(*Me*)–), 148.67 (C-2), 155.89 (C-4) ppm; MS (EI): $m/z$ (%) = 287 ($M^+$, 20), 259 (6), 216 (59), 204 (8), 196 (23), 118 (31), 113 (5), 91 (100).

*5-Methyl-1-[(E)-2-methyl-3-phenylallyloxymethyl]-6-azauracil* (**8f**, $C_{15}H_{17}N_3O_3$)

Colorless viscous oil; yield 0.177 g (62%); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.93$ (s, 3H, $CH_3$), 2.29 (s, 3H, $CH_3$), 4.24 (s, 2H, $CH_2$), 5.39 (s, 2H, $CH_2$), 6.56 (s, 1H, CH), 7.23–7.38 (m, 5H, $H_{arom}$), 10.19 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 15.43$ ($CH_3$), 16.22 ($CH_3$), 76.17 ($CH_2$), 78.71 ($CH_2$), 126.44, 127.80, 128.14, 130.03, 133.97, 137.59 ($C_{arom}$, CH, =C(*Me*)–), 144.39 (C-5), 149.07 (C-2), 156.58 (C-4) ppm; MS (EI): $m/z$ (%) = 287 ($M^+$, 8), 272 (11), 147 (62), 141 (24), 131 (100), 126 (5), 118 (6), 77 (21).

*1-[(E)-2-Methyl-3-phenylallyloxymethyl]-5-phenyl-6-azauracil* (**8g**, $C_{20}H_{19}N_3O_3$)

White solid; yield 0.237 g (68%); mp 134–135°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.94$ (s, 3H, $CH_3$), 4.32 (s, 2H, $CH_2$), 5.53 (s, 2H, $CH_2$), 6.60 (s, 1H, CH), 7.23–8.08 (m, 10H, $H_{arom}$), 10.29 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 15.48$ ($CH_3$), 76.36 ($CH_2$), 79.20 ($CH_2$), 126.68, 128.00, 128.17, 128.40, 128.41, 128.92, 130.47, 131.14, 133.94, 137.18 ($C_{arom}$, CH, =C(*Me*)–), 142.40 (C-5), 148.81 (C-2), 155.93 (C-4) ppm; MS (EI): $m/z$ (%) = 349 ($M^+$, 6), 203 (36), 190 (7), 160 (15), 147 (66), 131 (100), 115 (24), 104 (49), 91 (56).

*1-(Indan-2-yloxy)-6-azauracils **8h** and **8i***

6-Azauracil (**4b**, **4c**, 1 mmol) was stirred in 15 $cm^3$ dry acetonitrile under nitrogen and 0.87 $cm^3$ (*BSA* 3.5 mmol) were added. After a clear solution was obtained (10 min), the mixture was cooled to −50°C and 0.18 $cm^3$ (*TMS* triflate 1 mmol) were added followed by the dropwise addition of 0.56 g bis(indan-2-yloxy)methane (**7d**) (2 mmol). The reaction mixture was stirred at room temperature for 5 h, and quenched by addition of 5 $cm^3$ sat aq $NaHCO_3$ solution. The mixture was evaporated under reduced pressure and the residue was extracted with 3 × 50 $cm^3$ ether. The combined ether fractions were collected, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified on a silica gel column using 1/5 petroleum ether/chloroform to give **8h** and **8i**.

*5-Ethyl-1-(indan-2-yloxymethyl)-6-azauracil* (**8h**, $C_{15}H_{17}N_3O_3$)

White solid; yield 0.152 g (53%); mp 144–145°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.23$ (t, $J = 7.5$ Hz, 3H, $CH_3$), 2.68 (q, $J = 7.5$ Hz, 2H, $CH_2$), 3.03 (dd, $J = 4.5$, 16.0 Hz, 2H, 1′-H, 3′-H), 3.22 (dd, $J = 6.5$, 16.0 Hz, 2H, 1′-H, 3′-H); 4.65–4.69 (m, 1H, 2′-H), 5.42 (s, 2H, $CH_2$), 7.17–7.29 (m, 4H, $H_{arom}$), 9.51 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 10.41$ ($CH_3$), 23.28 ($CH_2$), 39.51 (C-1′, C-3′), 78.10 (C-2′), 79.76 ($CH_2$), 124.65, 126.69, 140.35 ($C_{arom}$), 148.12 (C-5), 148.83 (C-2), 156.18 (C-4) ppm; MS (EI): $m/z$ (%) = 287 ($M^+$, 7), 258 (6), 169 (19), 154 (61), 147 (9), 141 (6), 118 (93), 112 (11), 56 (100).

*1-(Indan-2-yloxymethyl)-5-phenyl-6-azauracil* (**8i**, $C_{19}H_{17}N_3O_3$)

White solid; yield 0.203 g (61%); mp 178–179°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 3.08$ (dd, $J = 4.4$, 15.9 Hz, 2H, I′-H, 3′-H), 3.25 (dd, $J = 6.5$, 15.9 Hz, 2H, 1′-H, 3′-H), 4.73 (m, 1H, 2′-H), 5.53 (s, 2H, $CH_2$), 7.17–8.06 (m, 9H, $H_{arom}$), 9.83 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 39.55$ (C-1′, C-3′), 78.50 (C-2′), 79.91 ($CH_2$), 124.68, 126.66, 126.72, 128.43, 130.51, 131.07, 140.33 ($C_{arom}$), 142.49 (C-5), 148.64 (C-2), 155.86 (C-4) ppm; MS (EI): $m/z$ (%) = 335 ($M^+$, 6), 202 (69), 190 (34), 160 (5), 147 (9), 131 (47), 118 (100), 105 (74).

*1-(3-Cyclohexen-1-ylmethoxymethyl)-5-phenyl-6-azauracil* (**8j**, $C_{17}H_{19}N_3O_3$)

5-Phenyl-6-azauracil (**4c**, 0.189 g, 1 mmol) was stirred in 15 $cm^3$ dry acetonitrile under nitrogen and 0.87 $cm^3$ (*BSA* 3.5 mmol) were added. After a clear solution was obtained (10 min), the mixture was cooled to −50°C and 0.18 $cm^3$ (*TMS* triflate 1 mmol) were added followed by the dropwise addition of 0.472 g bis(3-cyclohexen-1-ylmethoxy)methane (**7e**) (2 mmol). The reaction mixture was stirred at room temperature for 5 h, and worked up as described in preparation of **8h** and **8i** to give the title **8j**.

White solid; yield 0.199 g (64%); mp 128–129°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.27$–2.15 (m, 7H, 3 × $CH_2$, CH), 3.60 (dd, $J = 3.5$, 6.5 Hz, 2H, $CH_2$), 5.46 (s, 2H, $CH_2$), 5.64–5.67 (m, 2H, 2 × CH=), 7.28–7.47, 8.03–8.05 (2 × m, 5H, $H_{arom}$), 10.10 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 24.44$ ($CH_2$), 25.41 ($CH_2$), 28.27 ($CH_2$), 33.82 (CH), 75.12 ($CH_2$), 80.27 ($CH_2$), 125.73 (CH=), 127.07 (CH=), 128.37, 128.41, 130.43, 131.14 ($C_{arom}$), 142.34 (C-5), 148.80 (C-2), 156.00 (C-4) ppm; MS (EI): $m/z$ (%) = 313 ($M^+$, 29), 283 (6), 242 (5), 202 (41), 190 (43), 147 (4), 131 (100), 118 (13), 104 (82).

*1-(2-Cyclohexylethoxymethyl)-6-azauracils* (**8k**–**8m**)

6-Azauracils (**4a**–**4c**, 1 mmol) were stirred in 15 $cm^3$ dry acetonitrile under nitrogen and 0.87 $cm^3$ (*BSA* 3.5 mmol) were added. After a clear solution was obtained (10 min), the mixture was cooled to −50°C and 0.18 $cm^3$ *TMS* triflate 1 mmol were added followed by the dropwise addition of 0.536 g bis(2-cyclohexylethoxy)methane (**7f**) (2 mmol). The reaction mixture was stirred at room temperature for 5 h, and worked up as described in preparation of **8h** and **8i** to give **8k**–**8m**.

*1-(2-Cyclohexylethoxymethyl)-5-methyl-6-azauracil* (**8k**, $C_{13}H_{21}N_3O_3$)

Colorless viscous oil; yield 0.062 g (23%); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 0.87$–1.68 (m, 16H, $H_{hexyl}$, $CH_2$, $CH_3$), 3.62 (t, $J = 6.5$ Hz, 2H, $CH_2$), 5.25 (s, 2H, $CH_2$), 10.08 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz):

$\delta = 16.12$ ($CH_3$), 26.25, 26.54, 33.23, 34.32 ($C_{hexyl}$), 36.85 ($CH_2$), 68.05 ($CH_2$), 79.25 ($CH_2$), 144.26 (C-5), 149.20 (C-2), 156.86 (C-4) ppm; MS (EI): $m/z$ (%) = 267 ($M^+$, 5), 252 (7), 157 (18), 141 (69), 127 (21), 113 (6), 112 (9), 97 (6), 42 (100).

*1-(2-Cyclohexylethoxymethyl)-5-ethyl-6-azauracil*
(**8l**, $C_{14}H_{23}N_3O_3$)
Colorless viscous oil; yield 0.096 g (34%); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 0.91$–1.66 (m, 16H, $H_{hexyl}$, $CH_2$, $CH_3$), 2.63 (q, $J = 7.5$ Hz, 2H, $CH_2$), 3.64 (t, $J = 6.4$ Hz, 2H, $CH_2$), 5.29 (s, 2H, $CH_2$), 10.11 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 10.39$ ($CH_3$), 23.20 ($CH_2$), 26.20, 26.55, 33.23, 34.35 ($H_{hexyl}$), 36.86 ($CH_2$), 79.39 ($CH_2$), 147.92 (C-5), 149.05 (C-2), 156.46 (C-4) ppm; MS (EI): $m/z$ (%) = 281 ($M^+$, 7), 252 (8), 171 (13), 155 (84), 141 (26), 127 (9), 112 (4), 97 (6), 56 (100).

*1-(2-Cyclohexylethoxymethyl)-5-phenyl-6-azauracil*
(**8m**, $C_{18}H_{23}N_3O_3$)
White solid; yield 0.178 g (54%); mp 137–138°C; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 0.91$–1.53 (m, 13H, $H_{hexyl}$, $CH_2$), 3.74 (t, $J = 6.5$ Hz, 2H, $CH_2$), 5.44 (s, 2H, $CH_2$), 7.45–7.47, 8.04–8.05 (2 × m, 5H, $H_{arom}$), 10.09 (s, 1H, NH) ppm; $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 26.22$, 26.52, 33.27, 34.36 ($C_{hexyl}$), 36.80 ($CH_2$), 68.38 ($CH_2$), 79.95 ($CH_2$), 128.35, 128.41, 130.41, 131.14 ($C_{arom}$), 142.32 (C-5), 148.79 (C-2), 155.97 (C-4) ppm; MS (EI): $m/z$ (%) = 329 ($M^+$, 14), 219 (12), 203 (91), 189 (25), 175 (7), 160 (8), 131 (41), 104 (83), 53 (100).

*Determination of in vitro antimicrobial activity*
The primary screen was carried out using the agar disc-diffusion method [36] using *Müller-Hinton* agar medium. Sterile filter paper discs (8 mm diameter) were moistened with the compound solution in dimethylsulphoxide of specific concentration (200 $\mu$g/disc), the antibacterial antibiotic Ampicillin trihydrate (100 $\mu$g/disc) and the antifungal drug Clotrimazole (100 $\mu$g/disc) were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms. The plates were incubated at 37°C, and the diameter of the growth inhibition zones were measured after 24 h in case of bacteria and 48 h in case of *Candida albicans*.

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