Novel 5-(*N*-Alkylaminouracil) Acyclic Nucleosides

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Abstract: Protocols for the two-step syntheses of new 5-(*N*-hydroxyalkyl- and 5-*N*-benzylamino)uracil acyclic nucleosides bearing various functional groups (alkoxy/hydroxy and cyano/ester) are presented. Two groups of the title compounds were synthesised via aminolysis of 5-bromouracil and, subsequently, either coupling with an alkylating agent (2-chloromethoxyethyl acetate), or Michael-type addition to acrylonitrile/methyl acrylate. The reverse sequences for both syntheses were also studied. The target molecules were designed as non-nucleoside reverse transcriptase inhibitors (NNRTI) and are analogues of 1-(hydroxyethoxymethyl)-6-thiophenylthymine (HEPT) and 3-benzyl-1-cyanomethyluracils. The obtained compounds will be used in screening tests for anti-HIV-1 activity.

Key words: acyclic nucleosides, 5-(*N*-alkylamino)uracil, aminolysis, N-alkylation, Michael-type addition

Synthetic nucleosides are a class of compounds that are capable of mimicking natural nucleosides in a variety of metabolic pathways, and that therefore constitute attractive models for studies on interactions with molecular targets in living cells.[1] Acyclic nucleosides, which are distinguished representatives within the above group, have already been transferred from worldwide pharmaceutical laboratories into contemporary medicine. One of the best known examples —1-(hydroxyethoxymethyl)-6-thiophenylthymine (HEPT) — is a non-nucleoside reverse transcriptase inhibitor (NNRTI).[2] Acyclovir {9-[(2-hydroxyethoxy)methyl]guanine}[3] and Gancyclovir (9-{[(1,3-dihydroxypropan-2-yl)oxy]methyl}guanine),[4] which are drugs first marketed in 1982 and 1984 respectively, are still used in the treatment of HSV infections. Uramustine {5-[bis(2-chloroethyl)aminouracil]}, and other analogues of uracil mustards, exhibit a broad spectrum of antitumor activity and are used in the oral treatment of leukaemia.[5] In vitro studies revealed that 5-(*N*-[hydroxyalkyl]amino)- and 5-(*N*-arylamino)-1-(ω-hydroxyalkyl)uracil derivatives exhibit similar properties.[6] The structural resemblance of 5-(*N*-benzylamino)-1-(hydroxyethoxymethyl)uracil derivatives to the HEPT molecule (Figure 1) make them potential antiviral agents.[7] Its activity is significantly enhanced because the terminal hydroxy group on the alkyl substituent enables cellular phosphorylation to occur, similar to that observed with Acyclovir.[8]

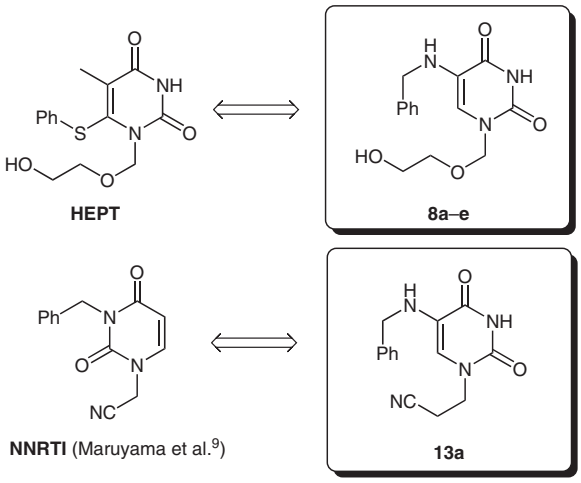

Figure 1 Examples of biologically active acyclic nucleosides and compounds synthesised in this work

An analogous relationship can be represented by 3-(3,5-dimethylbenzyl)-1-cyanomethyluracil, which is a very promising NNRTI agent found in the screening tests,[9] and 3-[5-(benzylamino)uracil-1-yl]propanenitrile (**13a**), which is one of the compounds synthesised in this work.

Based on these observations and the above structure–activity relationships, we present here a range of useful and versatile methods for the synthesis of non-functionalised and N-1-functionalised 5-[*N*-(hydroxyalkyl)amino]- and 5-(*N*-benzyloamino)uracil derivatives containing various (alkoxy, hydroxy, cyano, ester) groups in the alkyl backbone. The two target groups are not only a convenient and promising set of model compounds that can be used in the pursuit of novel, active antiviral agents but, due to the presence of simple functions, they include the possibility of further transformation into more complex structures. This operation is common practice for the optimisation of leading structures in initial pharmacological studies. The synthetic protocols presented here cover aminolysis of 5-bromouracil or its derivatives and a subsequent coupling or Michael-type addition to generate the target acyclic nucleosides.

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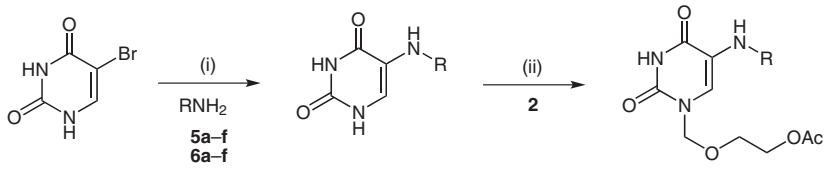


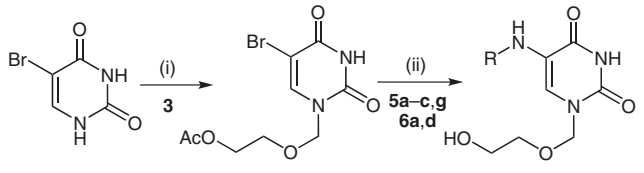
1 | 7a–f, 8a–f | 9a,c,e

5, 7	6, 8	9
a CH_2CH_2OH (96%)	**a** Bn (84%)	**a** Bn (51%)
b $CH_2CH_2CH_2OH$ (53%)	**b** 2,3-$Cl_2C_6H_3CH_2$ (30%)	**c** 2,4-$Cl_2C_6H_3CH_2$ (50%)
c $CH_2CH(OH)Me$ (83%)	**c** 2,4-$Cl_2C_6H_3CH_2$ (62%)	**e** 2,4-$F_2C_6H_3CH_2$ (33%)
d (*R*)-$CH(Et)CH_2OH$ (29%)	**d** 3,4-$Cl_2C_6H_3CH_2$ (76%)	
e $CH_2CH(OH)CH_2OH$ (54%)	**e** 2,4-$F_2C_6H_3CH_2$ (93%)	
f $CH_2CH_2NHCH_2CH_2OH$ (63%)	**f** 2,6-$F_2C_6H_3CH_2$ (20%)	

Scheme 1 *Reagents and conditions*: (i) RNH_2 (3–8 equiv), reflux: **5a–f**, 20–24 h, EtOH; **6a–f**, no solvent, N_2, 40 min, then MeOH, 10 min reflux; (ii) (1) HMDS (4 equiv), $(NH_4)_2SO_4$ cat., anhydrous MeCN, reflux 12 h; (2) 2-chloromethoxyethyl acetate (**2**), MeCN, r.t., 24 h.

In the initial synthetic approach, 5-(*N*-alkylamino)uracil derivatives were obtained in the reactions of 5-bromouracil (**1**) with the appropriate primary amines (Scheme 1).

Based on the previous research,[10–14] we improved the synthetic protocols and broadened the spectrum of the applied aminic reactants. The reactions of aminoalcohols **5a–f** with 5-bromouracil furnished 5-(hydroxyalkyl)aminouracil derivatives **7a–f** in moderate to high yields — the first subgroup of compounds, which are hitherto unknown. The aminolyses were run under an inert atmosphere in ethanol at reflux with 5-bromouracil (**1**) and four equivalents of amine. In the synthesis of 5-benzylaminouracil analogues **8a–f**, when 5-bromouracil (**1**) was heated with three equivalents of a suitable benzylamine **6a–f** in the absence of an additional solvent, the aminolyses proceeded in higher yields. The next step – the synthesis of 2-[(5-alkylaminouracil-1-yl)methoxy]ethyl acetates via coupling of alkylaminouracils with **3** – was ineffective and, therefore, the syntheses of the corresponding 1-alkyl-5-benzylaminouracil derivatives (**9a**, **9c** and **9e**) were performed in a 'one-pot' method. The syntheses comprised silylation of 5-benzylaminouracils **8a–d** using hexamethyldisilazane (HMDS) in boiling acetonitrile, followed by coupling with 2-chloromethoxyethyl acetate (**2**)[15] at ambient temperature. The final products were isolated in moderate yields.



1 | 4 (85%) | 10a–c,g, 11a,d

5, 10	6, 11
a CH_2CH_2OH (62%)	**a** Bn (51%)
b $CH_2CH_2CH_2OH$ (87%)	**d** 3,4-$Cl_2C_6H_3CH_2$ (37%)
c $CH_2CH(OH)Me$ (83%)	
g $CH_2CH{=}CH_2$ (78%)	

Scheme 2 *Reagents and conditions*: (i) BSA, TMSOTf; (ii) EtOH, reflux.

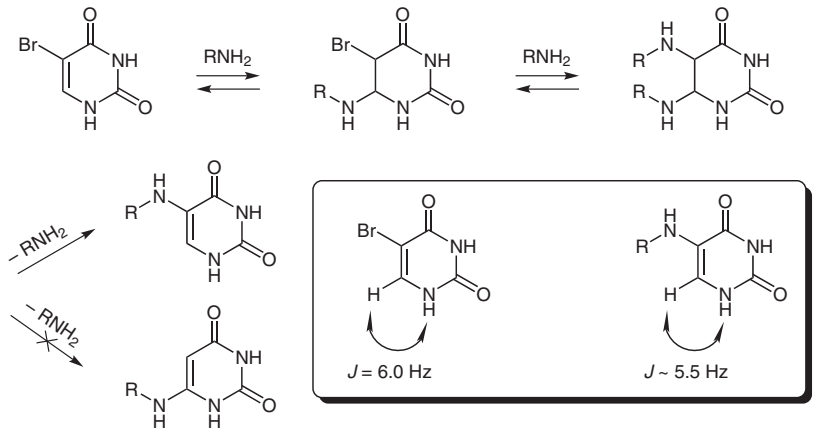
Syntheses of 1-(hydroxyethoxymethyl)-5-(hydroxyalkyl)aminouracil derivatives (**10a–c**,**g**, **11a**,**d**) were performed in a reverse sequence of steps. Here, the reactions proceeded via, firstly, N-1-alkylation of 5-bromouracil (**1**) with 2-acetoxymethoxyethyl acetate (**3**; Scheme 2) and subsequent aminolysis. 5-Bromouracil (**1**), after silylation with *N*,*O*-bis(trimethylsilyl)acetamide (BSA), was coupled with 2-acetoxymethoxyethyl acetate (**3**) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf). The use of 2-chloromethoxyethyl acetate (**2**) in the coupling reaction furnished the appropriate product in lower yields as compared to the first sequence. Additionally, in the aminolysis of 5-bromouracil derivative (**4**), deprotection of the acetoxy group occurred, although considering the structure of the target molecules, this behaviour was beneficial.

The final products from both reactions sequences were identified and characterised using typical spectroscopic methods. Taking into account the established mechanism of the reaction of aminolysis of 5-bromouracil[10] (Scheme 3), one could consider formation of 6-aminouracil derivatives instead of 5-aminouracil derivatives.

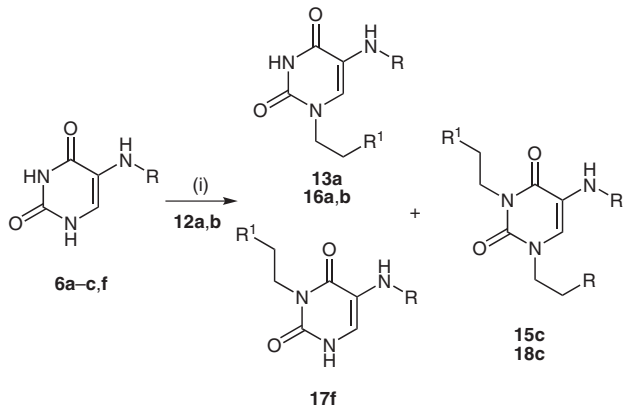
Nevertheless, the structures were verified by using 1D and 2D NMR spectroscopic protocols. ^1H–^1H COSY experiments confirmed that, in the case of **5** and **6**, a coupling between H-1 and H-6 uracil protons ($^3J_{H6–H1}$ ~ 5.5 Hz) was observed. This value was also found for 5-bromouracil ($^3J_{H6–H1}$ = 6.0 Hz). Moreover, the coupling diminished after N-1-substitution in derivatives **7** and **8**. It should be mentioned that, in both synthetic series, formation of N-3-alkylation products was not observed.

The synthesis of another group of acyclic nucleosides was achieved via a base-catalysed Michael-type addition of 5-benzylaminouracils to acrylic acceptors, namely methyl acrylate and acrylonitrile (Scheme 4).

Sodium hydride (NaH) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in anhydrous *N*,*N*-dimethylformamide



Scheme 3 Mechanism of aminolysis of 5-bromouracil, with coupling constants (^3J) for H-1 and H-6 protons in the uracil derivatives



12
a R = CN
b R = CO_2Me

13a R^1 = CN, R = Bn (46%)
15c R^1 = CN, R = 2,4-$Cl_2C_6H_3CH_2$ (74%)
16a R^1 = CO_2Me, R = Bn (80%)
16b R^1 = CO_2Me, R = 2,3-$Cl_2C_6H_3CH_2$ (45%)
17f R^1 = CO_2Me, R = 2,6-$F_2C_6H_3CH_2$ (45%)
18c R^1 = CO_2Me, R = R = 2,4-$Cl_2C_6H_3CH_2$ (49%)

Scheme 4 *Reagents and conditions*: (i) base (NaH or DBU), r.t., 2–48 h.

(DMF) were used as deprotonating agents. By controlling the temperature or reaction time, mono-N-1, N-3 or di-N-1,N-3 uracil adducts could be synthesised. A mechanism that accounts for the observed regioselectivity was published very recently.[16,17] Prolonged reaction time and/or increased temperature, in the presence of DBU as a deprotonating agent, led to selective formation of the N-3 adducts, whereas at room temperature, N-1 adducts were obtained. The reverse sequence of synthetic steps led to a retro-Michael reaction, which was published recently.[16,17]

In summary, we have synthesised two novel groups of 5-(*N*-alkylaminouracil) acyclic nucleosides via two-stage protocols covering aminolysis of 5-bromouracil and subsequent alkylation via either coupling of silylated uracils, or Michael-type addition. Furthermore, the reverse sequences of the reactions were applied, however, the efficiency for both groups of acyclic nucleosides was reduced — parallel deprotection and *retro*-Michael reactions were observed as undesired and dominating reactions, respectively. All the newly obtained compounds are currently being tested in terms of their antiviral anticancer activity and the results will be published elsewhere.

NMR spectra were recorded at 300 MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR with a Varian Inova 300 MHz; shift values (δ) are given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Elemental analyses were obtained with a Perkin–Elmer 240C apparatus. Mass spectra were recorded at ESI Bruker–Daltonics Amazon Mass Spectrometer and GC/MS Agilent Technologies 7890A/5975C. All reagents were purchased from Aldrich or Alfa Aesar. TLC $60F_{254}$ plates and silica gel 60 (0.040–0.063 mm) were purchased from Merck. Melting points were measured with a Boetius apparatus and are uncorrected. MeCN and DMF were distilled prior to use and stored over molecular sieves (4 Å).

2-Chloromethoxyethyl Acetate (2)

Reactant **2** was synthesised according to a previously described method.[18] To a stirred solution of 1,3-dioxolane (35 mL, 50.0 mmol) and anhydrous $ZnCl_2$ (0.10 g, 0.7 mmol), a solution of acetyl chloride (42 mL, 60.0 mmol) in anhydrous Et_2O (50 mL) was added dropwise. The reaction mixture was heated at reflux for 4 h, and then ether was distilled off and the oily residue was distilled under reduced pressure.

Yield: 42.00 g (61%); bp 78–81 °C/6 mmHg (Lit.[18] 74–76/5 mmHg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 3.88–3.91 (m, 2 H, CH_2), 4.26–4.29 (m, 2 H, CH_2), 5.23 (s, 2 H, CH_2).

2-Acetoxymethoxyethyl Acetate (3)

Reactant **3** was synthesized according to a previously described method.[19] To a stirred and cooled (–5 °C) solution of 1,3-dioxolane (23.5 mL, 35.0 mmol) and acetic anhydride (32.2 mL, 35 mmol), conc. H_2SO_4 (98%, d = 1.84 g·cm^{-3}, 0.2 mmol) was added dropwise. The reaction mixture was stirred at r.t. for 12 h, then sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with $CHCl_3$ (2 × 15 mL). The organic extract was dried over anhydrous Na_2SO_4, $CHCl_3$ was evaporated and the residue was distilled under reduced pressure.

Yield: 31.20 g (52%); bp 120–126 °C/10 mmHg (Lit.[20] 114–116 °C/10 mmHg).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08, 2.10 (2 × s, 6 H, CH_3), 3.84–3.87 (m, 2 H, CH_2), 4.21–4.24 (m, 2 H, CH_2), 5.29 (s, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4, 20.6, 62.9, 67.8, 88.7, 170.0, 170.4.

5-(2′-Hydroxyethylamino)uracil (7a); Typical Procedure

5-Bromouracil (**1**; 0.19 g, 1.0 mmol) and 2-aminoethanol (**4a**; 0.20 g, 4.0 mmol) were heated at reflux in EtOH (3 mL) for 24 h. The reaction mixture was allowed to cool to r.t. and the formed precipitate was filtered off, washed with cold EtOH and dried in air.

Yield: 0.16 g (96%); white solid; mp 112–113 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.86 (br d, *J* = 4.8 Hz, 2 H, H-1′), 3.55 (d, *J* = 5.4 Hz, 2 H, H-2′), 4.25 (br s, 1 H, NH′), 4.78 (t, *J* = 5.4 Hz, 1 H, OH), 6.37 (d, *J* = 5.5 Hz, 1 H, H-6), 10.18 (br d, *J* = 5.5 Hz, 1 H, NH-1), 11.16 (s, 1 H, N3-H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.1, 59.5, 112.8, 124.1, 149.5, 161.4.

Anal. Calcd for $C_6H_9N_3O_3$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.17; H, 5.18; N, 24.71.

5-(3′-Hydroxypropylamino)uracil (7b)

5-Bromouracil (**1**; 0.95 g, 5.0 mmol) and 3-aminopropanol (**5b**; 3.0 g, 40.0 mmol) were heated at reflux in EtOH (3 mL) for 20 h. EtOH was then evaporated and the oily residue was co-evaporated with H_2O (2 × 25 mL). The resulting solid was recrystallised from MeOH and the product was filtered off, washed with cold MeOH and dried in air.

Yield: 0.5 g (53%); white solid; mp 235–240 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.66 (m, 2 H, H-2′), 2.86 (q, *J* = 6.3 Hz, 2 H, H-1′), 3.47 (t, *J* = 6.3 Hz, 2 H, H-3′), 4.27 (t, *J* = 6.3 Hz, 1 H, NH), 4.57 (s, 1 H, OH), 6.26 (s, 1 H, H-6), 10.6 (br s, 2 H, N1-H, N3-H).

Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.03; H, 6.01; N, 22.63. Found: C, 45.32; H, 5.94; N, 22.82.

5-(2′-Hydroxypropylamino)uracil (7c)

5-Bromouracil (**1**; 0.95 g, 5.0 mmol) and 1-aminopropan-2-ol (**5c**; 3.0 g, 40.0 mmol) were heated at reflux in EtOH (3 mL) for 20 h. EtOH was evaporated and the oily residue was co-evaporated with H_2O (2 × 25 mL). The resulting solid was recrystallised from MeOH and the product was filtered off, washed with cold MeOH and dried in air.

Yield: 0.77 g (83%); white solid; mp 252–255 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.08 (d, *J* = 4.8 Hz, 3 H, H-3′), 2.56–2.82 (m, 2 H, H-1′), 3.72–3.85 (m, 1 H, H-2′), 4.20 (br s, 1 H, NH′), 4.80 (d, *J* = 6.3 Hz, 1 H, OH), 6.34 (d, *J* = 6.2 Hz, 1 H, H-6), 10.16 (br s, 1 H, NH-1), 11.15 (s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 20.7, 51.1, 63.4, 114.9, 121.8, 148.8, 160.5.

Anal. Calcd for $C_7H_{11}N_3O_3$: C, 45.03; H, 6.01; N, 22.63. Found: C, 45.25, H, 5.96; N, 22.78.

(*R*)-(+)-5-(1′-Hydroxymethylpropylamino)uracil (7d)

5-Bromouracil (**1**; 0.95 g, 5.0 mmol) and (*R*)-2-aminobutan-1-ol (**5d**; 3.6 g, 40.0 mmol) were heated at reflux in EtOH (3 mL) for 20 h. EtOH was then evaporated and the oily residue was co-evaporated with H_2O (2 × 25 mL). The resulting solid was recrystallised from MeOH and the product was filtered off, washed with cold MeOH and dried in air.

Yield: 0.29 g (29%); white solid; mp 227–228 °C; $[\alpha]_D^{20}$ +30 (*c* 5.00, DMSO).

^{1}H NMR (DMSO-d_6): δ = 0.85 (t, *J* = 7.5 Hz, 3 H, H-3′), 1.32–1.58 (m, 2 H, H-2′), 2.81–2.92 (m, 1 H, H-1′), 3.31–3.41 (m, 2 H, H-1″), 3.92 (d, *J* = 8.4 Hz, 1 H, NH), 4.63 (br s, 1 H, OH), 6.37 (s, 1 H, H-6), 10.20 (br s, 2 H, NH-1, N3-H).

Anal. Calcd for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58; N, 21.09. Found: C, 48.04; H, 6.77; N, 21.22.

5-(2′,3′-Dihydroxypropylamino)uracil (7e)

5-Bromouracil (**1**; 0.95 g, 5.0 mmol) and 3-aminopropane-1,2-diol (**5e**; 3.6 g, 40.0 mmol) were heated at reflux in EtOH (3 mL) for 20 h. EtOH was then evaporated and the oily residue was co-evaporated with H_2O (2 × 25 mL). The resulting solid was recrystallised from MeOH and the product was filtered off, washed with cold MeOH and dried in air.

Yield: 0.54 g (54%); white solid; mp 237–239 °C.

^{1}H NMR (DMSO-d_6): δ = 2.66–2.69 (m, 1 H, H-3′$_a$), 2.91–2.96 (m, 1 H, H-3′$_b$), 3.26–3.40 (m, 2 H, H-1′$_a$, H-1′$_b$), 3.55–3.60 (m, 1 H, H-2′), 4.20 (br s, 1 H, NH), 4.59 (t, *J* = 6.2 Hz, 1 H, OH), 4.87 (d, *J* = 6.3 Hz, 1 H, OH), 6.32 (d, *J* = 5.4 Hz, 1 H, H-6), 10.14 (br d, *J* = 4.8 Hz, 1 H, NH-1), 11.13 (s, 1 H, NH-3).

Anal. Calcd for $C_7H_{11}N_3O_4 \cdot 0.5H_2O$ (210.19): C, 40.10; H, 5.35; N, 20.27. Found: C, 39.98; H, 5.71; N, 20.15.

5-[2-(2-Hydroxyethylamino)ethylamino]uracil (7f)

5-Bromouracil (**1**; 0.19 g, 1.0 mmol) and 2-(2-aminoethylamino)ethanol (**5f**; 0.42 g, 4.0 mmol) were heated at reflux in EtOH (4 mL) for 24 h. The reaction mixture was cooled and the resulting precipitate was filtered off. The crude product was recrystallised from MeOH.

Yield: 0.14 g (63%); white solid; mp 206–207 °C (MeOH).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.57 (t, *J* = 5.4 Hz, 2 H, CH_2), 2.70 (t, *J* = 5.4 Hz, 2 H, CH_2), 2.83 (t, *J* = 5.4 Hz, 2 H, CH_2), 3.18 (br s, 1 H, NH), 3.44 (t, *J* = 5.4 Hz, 2 H, H-2″), 4.31 (br s, 2 H, OH, NH), 6.33 (s, 1 H, H-6), 8.23 (br s, 2 H, NH-1, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 40.3, 47.5, 51.3, 60.3, 112.5, 124.1, 149.3, 161.3.

Anal. Calcd for $C_8H_{14}N_4O_3$: C, 44.85; H, 6.59; N, 26.15. Found: C, 45.06; H, 6.46; N, 26.01.

5-(Benzylamino)uracil (8a)

5-Bromouracil (**1**; 1.00 g, 5.24 mmol) and benzylamine (**6a**; 1.5 mL, 15.0 mmol) were heated under a nitrogen atmosphere for 40 min. MeOH (20 mL) was then added and the reaction mixture was heated at reflux for 10 min. The formed precipitate was filtered off and washed with cold MeOH.

Yield: 0.96 g (84%); white solid; mp 280–283 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.14 (d, *J* = 6.3 Hz, 2 H, H-1′), 4.98 (t, *J* = 6.3 Hz, 1 H, NH′), 6.10 (s, 1 H, H-6), 7.19–7.26 (m, 1 H, PhH), 7.30 (s, 4 H, PhH), 10.21 (br s, 1 H, NH-3), 10.91 (br s, 1 H, NH-1).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 49.9, 112.9, 123.4, 126.8, 127.1 (2C), 128.3 (2C), 139.3, 161.4.

Anal. Calcd for $C_7H_{11}N_3O_3$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.78; H, 5.04; N, 19.65.

5-(2′,3′-Dichlorobenzylamino)uracil (8b)

5-Bromouracil (**1**; 1 mmol, 0.191 g) and 2,3-dichlorobenzylamine (**6b**; 2 mmol, 0.352 g) were mixed and heated to 160 °C. After 6 h, the reaction mixture was cooled and the residue was recrystallised from glacial AcOH (16 mL) with H_2O (1 mL).

Yield: 0.086 g (30%); white crystalline powder; mp 308–311 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.20 (d, *J* = 5.7 Hz, 2 H, CH_2), 5.21 (d, *J* = 6 Hz, 1 H, NH), 6.10 (d, *J* = 5.7 Hz, 1 H, H-6), 7.31 (t, *J* = 15 Hz, 1 H, H-5′), 7.31 (d, *J* = 7.9 Hz, 1 H, H-6′), 7.53 (d,

J = 6.6 Hz, 1 H, H-4′), 10.07 (d, *J* = 4.2 Hz, 1 H, NH-1), 11.24 (s, 1 H, NH-3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 45.4, 113.2, 123.0, 127.0, 128.1, 130.0, 131.7, 139.1, 149.4, 161.3.

Anal. Calcd for $C_{11}H_9Cl_2N_3O_2$: C, 46.18; H, 3.17; N, 14.69. Found: C, 46.13; H, 3.22; N, 14.44.

5-(2′,4′-Dichlorobenzylamino)uracil (8c)
Prepared as described above with 5-bromouracil (0.20 g, 1.05 mmol) and 2,4-dichlorobenzylamine (**6c**; 0.70 g, 4.0 mmol).

Yield: 0.18 g (62%); white solid; mp 296–299 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.14 (d, *J* = 6.3 Hz, 2 H, H-1′), 5.12 (t, *J* = 6.3 Hz, 1 H, NH′), 6.08 (s, 1 H, H-6), 7.32–7.41 (m, 2 H, PhH), 7.51 (s, 1 H, PhH), 10.05 (br s, 1 H, NH-3), 11.16 (br s, 1 H, NH-1).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 44.4, 113.2, 122.9, 127.4, 128.6, 129.9, 132.0, 133.0, 135.4, 149.3, 161.2.

Anal. Calcd for $C_{11}H_9Cl_2N_3O_2$: C, 46.18; H, 3.17; N, 14.69. Found: C, 45.98; H, 3.06; N, 14.79.

5-(3′,4′-Dichlorobenzylamino)uracil (8d)
Prepared as described above with 5-bromouracil (**1**; 0.2 g, 1.05 mmol) and 3,4-dichlorobenzylamine (**6d**; 0.70 g, 4.0 mmol).

Yield: 0.23 g (76%); white solid; mp 276–279 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.10 (d, *J* = 6.3 Hz, 2 H, H-1′), 5.21 (t, *J* = 6.3 Hz, 1 H, NH′), 6.13 (s, 1 H, H-6), 7.30 (dd, *J* = 1.8, 8.4 Hz, 1 H, PhH), 7.55–7.57 (m, 2 H, PhH), 10.03 (br s, 1 H, NH-3), 11.15 (br s, 1 H, NH-1).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.5, 113.2, 122.9, 127.4, 129.1, 129.2, 130.4, 130.9, 141.0, 149.2, 161.2.

Anal. Calcd for $C_{11}H_9Cl_2N_3O_2$: C, 46.18, H, 3.17; N, 14.69. Found: C, 46.55; H, 3.01; N, 14.54.

5-(2′,4′-Difluorobenzyloamino)uracil (8e)
Prepared as described above with 5-bromouracil (**1**; 0.22 g, 1.15 mmol) and 2,4-difluorobenzylamine (**6e**; 0.60 g, 4.2 mmol).

Yield: 0.23 g (93%); grey solid; mp 304–305 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.11 (d, *J* = 6.0 Hz, 2 H, H-1′), 4.91 (t, *J* = 6.0 Hz, 1 H, NH′), 6.21 (d, *J* = 2.7 Hz, 1 H, H-6), 7.01–7.07 (m, 1 H, PhH), 7.14–7.22 (m, 1 H, PhH), 7.34–7.43 (m, 1 H, PhH), 10.09 (br s, 1 H, NH-3), 11.16 (br s, 1 H, NH-1).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 40.2, 103.6 (t, J_{C-F} = 25.9 Hz), 111.3 (dd, J_{C-F} = 3.6, 21.0 Hz), 113.2, 122.2 (dd, J_{C-F} = 3.6, 15.0 Hz), 122.9, 130.4 (dd, J_{C-F} = 6.3, 9.7 Hz), 149.3, 160.1 (dd, J_{C-F} = 12.3, 246 Hz), 161.2, 161.3 (dd, J_{C-F} = 12.2, 245.2 Hz).

MS (EI, 60 eV): *m*/*z* (%) = 253 (16) [M]$^+$, 127 (100).

Anal. Calcd for $C_{11}H_9F_2N_3O_2$: C, 52.18; H, 3.58; N, 16.60. Found: C, 51.56; H, 3.47; N, 16.27.

5-(2′,6′-Difluorobenzylamino)uracil (8f)
5-Bromouracil (**1**; 1.16 mmol, 0.22 g), 2,6-difluorobenzylamine (**6f**; 3.5 mmol, 0.50 g) and *n*-butanol (5 mL) were mixed and heated to reflux. After 6 h, the reaction mixture was cooled and dried under vacuum. The residue was recrystallised form glacial AcOH (8 mL) containing a few drops of H_2O.

Yield: 0.06 g (20%); white crystalline powder; mp 276–278 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.13 (d, *J* = 5.4 Hz, 2 H, CH_2), 4.41 (d, *J* = 6.0 Hz, 1 H, NH), 6.50 (d, *J* = 5.7 Hz, 1 H, H-6), 7.10 (t, *J* = 8.1 Hz, 2 H, H-3′,5′), 7.40 (quint, *J* = 8.4 Hz, 1 H, H-4′), 10.23 (d, *J* = 4.5 Hz, NH-1), 11.53 (s, 1 H, NH-3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 35.6, 111.4, 111.8, 114.3, 122.8, 130.0, 142.2, 149.4, 150.9, 160.1, 161.3.

Anal. Calcd for $C_{11}H_9F_2N_3O_2$: C, 52.18; H, 3.58; N, 16.60. Found: C, 52.34; H, 3.39; N, 16.55.

1-(2′-Acetoxyethoxymethyl)-5-(benzylamino)uracil (9a); Typical Procedure
A suspension of 5-benzylaminouracil (**8a**; 0.11 g, 0.5 mmol), $(NH_4)_2SO_4$ (2 mg) and HMDS (0.43 mL, 2.0 mmol) in anhydrous MeCN (5 mL) was heated at reflux for 12 h. The reaction mixture was cooled to r.t. and 2-chloromethoxyethyl acetate (**2**; 0.16 g, 1.0 mmol) in anhydrous MeCN (0.5 mL) was added. The reaction mixture was stirred at r.t. for 24 h then quenched by pouring into 5% aq $NaHCO_3$ (15 mL) and extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated to give an oily residue. The product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 3%).

Yield: 0.09 g (51%); white solid; mp 107–110 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, CH_3), 3.60–3.63 (m, 2 H, CH_2), 4.06–4.09 (m, 4 H, CH_2, H-1′), 4.40 (br s, 1 H, NH‴), 5.05 (s, 2 H, H-1″), 6.14 (s, 1 H, H-6), 7.19–7.30 (m, 5 H, PhH), 9.89 (br s, 1 H, NH-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 48.3, 63.1, 67.2, 76.8, 113.9, 125.6, 127.5, 127.8, 128.9, 137.5, 149.6, 160.9, 170.9.

Anal. Calcd for $C_{16}H_{19}N_3O_5$: C, 57.65; H, 5.75; N, 14.61. Found: C, 57.28; H, 5.82; N, 14.50.

1-(2′-Acetoxyethoxymethyl)-5-(2″,4″-dichlorobenzylamino)uracil (9c)
Prepared as described above with 5-(2,4-dichlorobenzylamino)uracil (**8c**; 0.10 g, 0.35 mmol).

Yield: 0.07 g (50%); waxy yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3), 3.71–3.74 (m, 2 H, CH_2), 4.16–4.24 (m, 4 H, CH_2, H-1′), 4.60 (br s, 1 H, NH″), 5.13 (s, 2 H, H-1″), 6.20 (s, 1 H, H-6), 7.23 (dd, *J* = 2.4, 8.4 Hz, 1 H, PhH), 7.30 (d, *J* = 8.4 Hz, 1 H, PhH), 7.41 (d, *J* = 2.4 Hz, 1 H, PhH), 10.11 (br s, 1 H, NH-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 45.3, 63.1, 67.3, 76.8, 114.3, 125.2, 127.5, 129.6, 129.7, 133.6, 134.0, 134.1, 149.6, 160.8, 170.9.

MS (EI, 70 eV): *m*/*z* (%) = 403 (14) [M]$^+$, 401 (21) [M]$^+$, 87 (100).

1-(2′-Acetoxyethoxymethyl)-5-(2″,4″-difluorobenzylamino)uracil (9e)
Prepared as described above with 5-(2,4-dichlorobenzylamino)uracil (**8e**; 0.10 g, 0.40 mmol).

Yield: 0.05 g (33%); waxy yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3), 3.70–3.74 (m, 2 H, CH_2), 4.15–4.18 (m, 4 H, CH_2, H-1′), 4.47 (br s, 1 H, NH″), 5.13 (s, 2 H, H-1″), 6.30 (s, 1 H, H-6), 6.80–6.90 (m, 2 H, PhH), 7.29 (m, 1 H, PhH), 10.86 (br s, 1 H, NH-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 40.9 (d, J_{C-F} = 3.6 Hz), 62.8, 66.8, 76.4, 103.7 (t, J_{C-F} = 25.5 Hz), 111.2 (dd, J_{C-F} = 3.7, 21.1 Hz), 114.0, 120.5 (dd, *J* = 3.8 Hz, J_{C-F} = 14.9 Hz), 124.8, 130.4 (dd, J_{C-F} = 5.9, 9.6 Hz), 149.4, 160.5 (dd, J_{C-F} = 11.9, 248.7 Hz), 160.7, 162.1 (dd, J_{C-F} = 11.9, 248.5 Hz).

MS (EI, 70 eV): *m*/*z* (%) = 369 (34) [M]$^+$, 127 (100).

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (4)
The product was obtained through a modified method described in the literature.[21] To a suspension of 5-bromouracil (**1**; 1.91 g, 10 mmol) in anhydrous MeCN (30 mL), BSA (3 mL, 12 mmol) was added. The reaction mixture was stirred for 12 h until the suspension

clarified, an additional portion of BSA (1.5 mL, 6.0 mmol) was added and the mixture was stirred for a further 3 h. Subsequently, 2-acetoxymethoxyethyl acetate (**3**; 3.5 g, 20 mmol) was added, followed by TMSOTf (0.34 mL, 2.0 mmol) addition. The reaction mixture was stirred for 24 h, then quenched with 5% aq $NaHCO_3$ and extracted with EtOAc (4 × 20 mL). The organic layer was dried over $MgSO_4$ and evaporated to an oily residue. The product was purified by silica gel column chromatography (MeOH–$CHCl_3$, 0→5%).

Yield: 2.62 g (85%); white solid; mp 112–113 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 3.81–3.84 (m, 2 H, CH_2), 4.22–4.25 (m, 2 H, CH_2), 5.23 (s, 2 H, CH_2–1′), 7.73 (s, 1 H, H-6), 10.04 (s, 1 H, N3-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 63.0, 67.9, 77.0, 97.8, 142.6, 150.8, 159.5, 171.0.

Anal. Calcd for $C_9H_{11}BrN_2O_5$: C, 35.20; H, 3.61; N, 9.12. Found: C, 35.35; H, 3.49; N, 9.31.

1-(2′-Hydroxyethoxymethyl)-5-(2″-hydroxyethylamino)uracil (10a)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.60 g, 2.0 mmol) and 2-aminoethanol (**5a**; 0.40 g, 8.0 mmol) were heated at reflux in EtOH (5 mL) for 24 h. The reaction mixture was evaporated to an oily residue and the product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 5→20%).

Yield: 0.29 g (62%); white solid; mp 110–113 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.89 (q, J = 5.7 Hz, 2 H, H-1″), 3.48 (s, 2 H, CH_2), 3.49 (s, 2 H, CH_2), 3.57 (q, J = 5.4 Hz, 2 H, H-2″), 4.40 (t, J = 5.7 Hz, 1 H, OH), 4.66 (m, 1 H, NH″), 4.78 (t, J = 5.4 Hz, 1 H, OH), 5.07 (s, 2 H, H-1′), 6.66 (s, 1 H, H-6), 11.45 (s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.0, 59.0, 60.0, 70.3, 76.4, 115.4, 124.8, 149.2, 160. 9.

Anal. Calcd for $C_9H_{15}F_2N_3O_5$: C, 44.08; H, 6.17; N, 17.13. Found: C, 44.00; H, 6.15; N 16.92.

1-(2′-Hydroxyethoxymethyl)-5-(3″-hydroxypropylamino)uracil (10b)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.30 g, 1.0 mmol) and 3-aminopropanol (**5b**; 0.25 g, 4.0 mmol) were heated at reflux in EtOH (3 mL) for 24 h. The reaction mixture was evaporated to an oily residue and the product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 5→10%).

Yield: 0.26 g (87%); white solid; mp 121–123 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.69 (quin, J = 6.3, 2 H, H-2″), 2.88 (dt, J = 6.3, 6.0 Hz, 2 H, H-1″), 3.4–3.5 (m, 6 H, H-3′, H-4′, H-3″), 4.48 (t, J = 6.0 Hz, 1 H, OH-3″), 4.52 (t, 1 H, J = 4.8 Hz, OH-4′), 4.65 (m, 1 H, NH″), 5.07 (s, 2 H, H-1′), 6.56 (s, 1 H, H-6), 11.40 (s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 31.0, 40.9, 59.0, 60.0, 70.2, 76.3, 114.7, 124.9, 149.2, 160.8.

MS (EI, 70 eV): m/z (%) = 259 (17) $[M]^+$, 140 (100).

1-(2′-Hydroxyethoxymethyl)-5-(2″-hydroxypropylamino)uracil (10c)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.59 g, 1.9 mmol) and 1-aminopropan-2-ol (**5c**; 0.50 g, 8.0 mmol) were heated at reflux in EtOH (5 mL) for 28 h. The reaction mixture was evaporated to an oily residue and the product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 5→10%).

Yield: 0.39 g (83%); reddish solid; mp 133–135 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.10 (d, J = 6.0 Hz, 3 H, H-2″), 2.64 (m, 1 H, H-1″$_a$), 2.85 (m, 1 H, H-1″$_b$), 3.48, 3.49 (2 × s, 4 H, H-3′, H-4′), 3.82 (m, 1 H, H-2″), 4.35 (dd, J = 4.2, 7.5 Hz, 1 H, NH″), 4.66 (m, 1 H, OH-5′), 4.83 (d, J = 4.8 Hz, 1 H, OH-3″), 5.07 (s, 2 H, H-1′), 6.65 (s, 1 H, H-6), 11.45 (s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 21.5, 51.2, 60.0, 64.3, 70.3, 76.4, 115.4, 124.8, 149.2, 160.9.

MS (EI, 70 eV): m/z (%) = 259 (14) $[M]^+$, 245 (100).

1-(2′-Hydroxyethoxymethyl)-5-(allylamino)uracil (10g)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.30 g, 1.0 mmol) and allylamine (**5g**; 0.228 g, 4.0 mmol) were heated at reflux in EtOH (2 mL) for 24 h. The reaction mixture was evaporated to dryness and the residue was recrystallised from MeOH to give the first crop of product (0.10 g). An additional fraction **10g** (0.07 g) was isolated from the filtrate using silica gel column chromatography (MeOH–$CHCl_3$, 0→5%).

Total yield: 0.17 g (78%); mp 141–142 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.47 (s, 2 H, CH_2), 3.48 (s, 2 H, CH_2), 3.53 (m, 2 H, H-1″), 4.62–4.70 (m, 2 H, NH″, OH), 5.05 (s, 2 H, H-1′), 5.09–5.23 (m, 2 H, H-4″), 5.83 (m, 1 H, H-2″), 6.56 (s, 1 H, H-6), 11.44 (s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 45.7, 60.0, 70.3, 76.4, 115.6, 115.8, 124.2, 135.1, 149.1, 160.8.

Anal. Calcd for $C_{10}H_{15}N_3O_4$: C, 49.79; H, 6.27; N, 17.42. Found: C, 49.44; H, 6.23; N, 17.29.

1-(2′-Hydroxyethoxymethyl)-5-(benzylamino)uracil (11a)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.30 g, 1.0 mmol) and benzylamine (**6a**; 0.43 g, 4.0 mmol) were heated at reflux in EtOH (3 mL) under nitrogen for 30 h. The reaction mixture was evaporated to dryness and the product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 0→5%).

Yield: 0.15 g (51%); white solid; mp 154–156 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.34 (t, J = 4.5 Hz, 2 H, CH_2), 3.40 (t, J = 4.5 Hz, 2 H, CH_2), 4.11 (d, J = 6.3 Hz, 2 H, H-1″), 4.99 (s, 2 H, H-1′), 5.10 (t, J = 6.3 Hz, 1 H, NH″), 6.50 (s, 1 H, H-6), 7.21–7.33 (m, 5 H, PhH), 10.20 (br s, 1 H, NH-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 46.8, 60.0, 70.2, 76.4, 115.7, 124.1, 126.8, 127.3, 128.3, 139.0, 149.1, 160.8.

MS (EI, 70 eV): m/z (%) = 291 (11) $[M]^+$, 91 (100).

1-(2′-Acetoxyethoxymethyl)-5-(3″,4″-dichlorobenzylamino)uracil (11d)

1-(2′-Acetoxyethoxymethyl)-5-bromouracil (**4**; 0.17 g, 0.56 mmol) and 3,4-dichlorobenzylamine (**6d**; 0.43 g, 2.8 mmol) were heated at reflux in EtOH (3 mL) under nitrogen for 30 h. The reaction mixture was evaporated to dryness and the product was isolated by silica gel column chromatography (MeOH–$CHCl_3$, 3%).

Yield: 0.08 g (37%); reddish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, CH_3), 3.70–3.73 (m, 2 H, CH_2), 4.15–4.19 (m, 4 H, CH_2, H-1′), 4.53 (br s, 1 H, NH″), 5.11 (s, 2 H, H-1″), 6.17 (s, 1 H, H-6), 7.16 (dd, J = 2.1, 8.4 Hz, 1 H, PhH), 7.41–7.46 (m, 2 H, PhH), 9.76 (br s, 1 H, NH-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 47.2, 63.1, 67.4, 76.9, 114.4, 125.2, 126.6, 129.2, 130.9, 131.8, 133.1, 138.0, 149.9, 160.7, 170.9.

MS (EI, 70 eV): m/z (%) = 403 (13) $[M]^+$, 401 (20) $[M]^+$, 87 (100).

Michael-Type Addition with NaH as Deprotonating Agent; General Procedure

The 5-aminouracil derivative was dissolved in DMF (8 mL) and stirred in a round-bottom flask whilst NaH (80% in mineral oil, 1 equiv) was introduced. Methyl acrylate was added in the appropriate ratio with respect to uracil derivative and, after 2 h, the reaction

was quenched with 5% aq HCl and volatiles were removed under reduced pressure. The final products were purified by column chromatography (MeOH–$CHCl_3$, 3%).

3-[5-(Benzylamino)uracil-1-yl]propanenitrile (13a)
Prepared as described above with 5-(benzylamino)uracil (**8a**; 0.22 g, 1 mmol) and acrylonitrile (0.10 mL, 1.5 mmol).

Yield: 0.10 g (46%); white solid; mp 125–130 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.83 (t, *J* = 6.6 Hz, 2 H, H-2′), 3.84 (t, *J* = 6.6 Hz, 2 H, H-1′), 4.11 (d, *J* = 6.4 Hz, 2 H, NHCH_2), 5.00 (t, *J* = 6.4 Hz, 1 H, N*H*CH_2), 6.64 (s, 1 H, H-6), 7.29–7.36 (m, 5 H, PhH), 11.49 (s, 1 H, H-3).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 16.6, 42.9, 46.9, 116.1, 118.3, 124.3, 126.9, 127.5, 128.3, 139.0, 148.53, 160.70.

MS (EI, 25 eV): *m*/*z* (%) = 271 (100) $[M + H]^+$.

3,3′-[5-(2,4-Dichlorobenzylamino)uracil-1,3-diyl]dipropanenitrile (15c)
Prepared as described above with 5-(2,4-dichlorobenzylamino)uracil (**8c**; 0.29 mmol, 0.084 g) and acrylonitrile (0.59 mmol, 0.038 mL).

Yield: 0.072 g (74%); white solid; mp 119–122 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.90 (t, *J* = 5.7 Hz, 2 H, CH_2), 4.10 (d, *J* = 6.3 Hz, 2 H, CH_2), 4.15 (t, *J* = 5.7 Hz, 2 H, CH_2), 5.40 (s, 1 H, NH), 6.67 (s, 1 H, H-6), 7.31 (d, *J* = 8.1 Hz, 1 H, H-5′), 7.34 (d, *J* = 8.1 Hz, 1 H, H-6′), 7.57 (s, 1 H, H-3′).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 15.6, 16.5, 36.6, 44.2, 44.4, 115.7, 118.4, 123.4, 127.3, 128.6, 129.8, 132.1, 133.0, 135.2, 148.3, 159.4.

MS (EI, 25 eV): *m*/*z* (%) = 392.1 (100) $[M]^+$, 394.1 (61) $[M]^+$, 288.3 (58).

Michael-Type Addition with DBU as Deprotonating Agent; General Procedure
5-Aminouracil derivative was dissolved in DMF (8 mL) and stirred in a round-bottom flask whilst DBU (1 equiv) was introduced. Methyl acrylate (1 equiv) was added and, after 2 h, the reaction was quenched with 5% aq HCl and the volatiles were removed under reduced pressure. The final products were purified using column chromatography (MeOH–$CHCl_3$, 3%).

Methyl 3-[5-(Benzylamino)uracil-1-yl]propanoate (16a)
Yield: 80%; white solid; mp 136–138 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.58 (t, *J* = 6.9 Hz, 2 H, CH_2), 3.53 (s, 3 H, CH_3), 3.78 (t, *J* = 6.9 Hz, 3 H, CH_2), 4.08 (d, *J* = 6.3 Hz, 1 H, NH), 6.53 (s, 1 H, H-6), 7.34–7.24 (m, 5 H, PhH), 11.39 (s, 1 H, N-3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 32.7, 43.6, 46.8, 51.5, 117.0, 124.0, 126.8, 127.4, 128.3, 139.1, 148.5, 160.8, 171.1.

MS (EI, 25 eV): *m*/*z* (%) = 304.1 (100) $[M + H]^+$.

Methyl 3-[5-(2,3-Dichlorobenzylamino)uracil-1-yl]propanoate (16b)
Yield: 45%; white solid; mp 174–177 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.53 (s, 3 H, CH_3), 3.78 (t, *J* = 6.6 Hz, 2 H, CH_2), 4.21 (d, *J* = 6 Hz, 2 H, CH_2), 5.28 (t, *J* = 6.6 Hz, 1 H, NH), 6.52 (s, 1 H, H-6), 7.32 (t, *J* = 17.7 Hz, 1 H, H-5′), 7.31 (d, *J* = 18 Hz, 1 H, H-6′), 7.53 (d, *J* = 6.6 Hz, 1 H, H-4′), 11.47 (s, 1 H, NH-3).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 32.7, 43.6, 45.4, 51.4, 117.2, 123.6, 126.8, 128.1, 128.8, 130.0, 131.6, 138.9, 148.6, 160.7, 171.1.

MS (EI, 25 eV): *m*/*z* (%) = 372.1 (100) $[M + H]^+$, 373.1 (16), 374.1 (64).

Methyl 3-[5-(2,6-Difluorobenzylamino)uracil-3-yl]propanoate (17f)
Yield: 45%; white solid; mp 102–104 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.52 (t, *J* = 7.5 Hz, 2 H, CH_2), 3.56 (s, 3 H, CH_3), 4.02 (t, *J* = 7.2 Hz, 2 H, CH_2), 4.14 (d, *J* = 6.3 Hz, 2 H, CH_2), 4.54 (t, *J* = 6.3 Hz, 1 H, NH), 6.55 (d, *J* = 5.7 Hz, 1 H, H-6), 7.10 (t, *J* = 7.8 Hz, 2 H, H-3′,5′), 7.40 (quint, *J* = 7.8 Hz, 1 H, H-4′), 10.60 (d, *J* = 5.4 Hz, 1 H, NH-1).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 31.8, 35.5, 36.2, 51.5, 111.5, 111.8, 113.0, 114.2, 122.4, 130.1, 143.5, 149.0, 160.3, 171.2.

Anal. Calcd for $C_{15}H_{15}F_2N_3O_4$: C, 53.10; H, 4.46; N, 12.38. Found: C, 53.25; H, 4.59; N, 12.51.

Dimethyl 3,3′-[5-(2,4-Dichlorobenzylamino)uracil-1,3-diyl]dipropanoate (18c)
Yield: 49%; white solid; mp 177–179 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.50 (t, *J* = 1.8 Hz, 2 H, CH_2), 2.58 (t, *J* = 7.2 Hz, 2 H, CH_2), 3.42 (s, 3 H, CH_3), 3.77 (t, *J* = 6.9 Hz, 2 H, CH_2), 4.14 (d, *J* = 6.3 Hz, 2 H, CH_2), 5.19 (t, *J* = 6.9 Hz, 1 H, NH), 5.48 (s, 1 H, H-6), 7.32 (d, *J* = 8.4 Hz, 1 H, H-6′), 7.39 (d, *J* = 8.4 Hz, 1 H, H-5′), 7.59 (s, 1 H, H-3′).

^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 28.0, 30.5, 32.6, 35.5, 44.3, 51.4, 58.6, 95.4, 117.3, 123.6, 127.3, 128.6, 129.8, 135.3, 148.6, 160.6, 171.1.

MS (EI, 25 eV): *m*/*z* (%) = 458.1 (100) $[M]^+$, 460.1 (64) $[M]^+$.

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