HETEROCYCLES, Vol. 94, No. 5, 2017, pp. 912 - 922. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 12th March, 2017, Accepted, 11th April, 2017, Published online, 27th April, 2017
DOI: 10.3987/COM-17-13696

SELECTIVE N^1-ALKYLATION OF 1,3-DIBENZOYLURACILS: ONE-POT WAY TO N^1-MONOSUBSTITUTED URACIL DERIVATIVES

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Abstract – A new method for synthesis of N^1-monosubstituted uracils and 5- and 6-methyluracil derivatives was developed. It consists in the selective N^1-deprotection of N^1,N^3-dibenzoyluracils in anhydrous dimethylformamide in the presence of potassium carbonate at room temperature and subsequent N^1-alkylation by allyl, benzyl or phenacyl type halides or by primary alcohols toluenesulfonates conducted *one-pot* without isolation of the intermediates. Final N^3-debenzoylation by aqueous-alcoholic solution of ammonia affords the corresponding N^1-monosubstituted uracil derivatives with overall yields of 52-84%.

INTRODUCTION

N-Substituted uracil derivatives have a broad spectrum of biological activity. In particular, effective antineoplastic agents,[1,2] inhibitors of viral replication,[3-6] antibacterial agents[7,8] and blockers of protozoa lifecycle[9,10] were found among the compounds of this series. There are two fundamentally different methods of formation of N-C bond in pyrimidines. The first method uses alkylated or protected bases and leads to the formation of quaternary salts. It is based on the donor-acceptor interaction between the lone pair electrons of nitrogen atom and carbocation. An example of this method is the classical Hilbert-Johnson reaction. The second method includes a preliminary ionization by treatment of non-protected uracil and its derivatives with a base (e.g., K_2CO_3, NaOH, NaH, *t*-BuOK etc.).

Silyl variant of the Hilbert-Johnson reaction is widely used in the synthesis of pyrimidine nucleoside.[11,12] Silylated bases are also used in synthesis of acyclic nucleoside analogues.[13,14] This method is based on the

condensation of trimethylsilyluracil derivatives with highly reactive alkylating agents (for example, α-halogen ethers or halogen sugars) in an aprotic solvent under mild conditions. The condensation proceeds successfully with allyl bromide,[15] propargyl bromide,[16] cinnamyl bromide[17] or benzyl halides[16,18] heating under reflux in 1,2-dichloroethane. Heating of 2,4-bis(trimethylsilyloxy)pyrimidines with an excess of α,ω-dibromoalkanes leads to the formation of N^1-(ω-bromoalkyl)uracil derivatives in good yields.[19-21] This method can also be extended to alkylating agents with a low reactivity, such as (2-aryloxy)ethyl bromide.[5] However, these cases require more harsh synthetic conditions: heating a mixture of a substrate and an alkylating agent at temperatures up to 180 °C without a solvent. The presence of a substituent in the 6-position of the pyrimidine ring can change the regioselectivity of the alkylation[22] or give a mixture of N^1-, N^3-mono and N^1,N^3-disubstituted 6-R-uracils, the ratio of which depends on reaction conditions.[23] Furthermore, certain functional groups may be decomposed under stringent conditions and that significantly limits the application of this method.

The second method of N-substituted uracil derivatives synthesis is based on the reaction of an uracil salt with alkylating agents having medium or low reactivity. The reaction proceeds in a polar aprotic solvent which is capable of solvating the salt form.[24,25] Highly reactive alkylating agents are rarely used in this method because of their unstability in a polar medium and in the presence of bases. Another disadvantage of this method is the formation of a mixture of N^1-mono- and N^1,N^3-disubstituted derivatives, which often require chromatographic separation.[24] The formation of N^3- or O^4-substituted uracil derivatives is also described.[26-28] In the case of uracils having a substituent at the 6-position, the shift of the products ratio is observed toward the formation of N^1,N^3-disubstituted derivatives. In this context, the development of a selective method of introduction of substituents in position 1 of uracil residue seems an actual task.

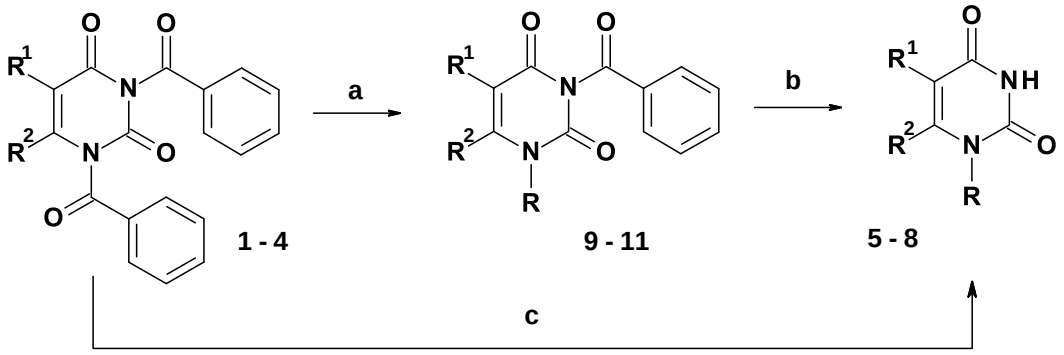
Benzoyl protection of the pyrimidine ring 3-position in the synthesis of N^1-substituted derivative of uracil, thymine[29] and 5-fluorouracil[30] is described in the literature. 1-Substituted 3-benzoyl derivatives, which are formed in this case, are readily debenzoylated under alkaline hydrolysis. The starting N^3-benzoyluracil derivatives are obtained by the selective N^1-debenzoylation of the corresponding N^1,N^3-dibenzoyl derivatives at room temperature using ammonium hydroxide in aqueous alcohol,[31] potassium carbonate in aqueous dioxane,[32] or adding water to the reaction mixture at the end of the benzoylation reaction.[33] However, selective formation of N^3-benzoyl-6-methyluracil in the hydrolysis does not occur in the case of N^1,N^3-dibenzoyl-6-methyluracil, the only product is completely deblocked 6-methyluracil.[34]

High lability of N^1-benzoyl substituent in N^1,N^3-dibenzoyluracil prompted us to investigate the possibility of direct use of this substrate in the N-alkylation reactions to obtain N^1-monosubstituted uracil derivatives and analogues thereof selectively.

RESULTS AND DISCUSSION

We have found that interaction of equimolar amounts of 1,3-dibenzoyluracil derivatives (**1-4**) and *p*-toluenesulfonate of 2-(2-naphthyloxy)ethanol in the presence of excess potassium carbonate in anhydrous DMF at room temperature for 24 h, followed by crystallization of the reaction product from 90% EtOH containing 2.5% ammonium hydroxide,[31] leads to 1-[2-(2-naphthyloxy)ethyl]uracil derivative (**5-8**) with yields of 61-78%. Products of N^1,N^3-substitution were not formed (according to TLC) (Scheme 1).

It was found that using acetone without addition of ammonium hydroxide for recrystallization of the alkylation products of 1,3-dibenzoyluracils (**1-3**) by 2-(2-naphthyloxy)ethanol *p*-toluenesulfonate gave intermediate 1-[2-(2-naphthyloxy)ethyl]-3-benzoyluracil derivatives (**9-11**) with the yield of 54-77%. Compounds **9-11** were refluxed in EtOH solution of ammonium and gave the final debenzoylation products (**5-7**) with yields of 94-95% (Scheme 1).



1, 5, 9 $R^1 = R^2 = H$
2, 6, 10 $R^1 = Me$, $R^2 = H$
3, 7, 11 $R^1 = H$, $R^2 = Me$
4, 8 $R^1 = R^2 = Me$
5-11 $R = CH_2CH_2O(2\text{-}C_{10}H_7)$

Scheme 1. Reagents and conditions: (**a**) $TsOCH_2CH_2O(2\text{-}C_{10}H_7)$, K_2CO_3, DMF, 25 °C, 24 h, 54-77%; (**b**) NH_4OH, 90% EtOH, reflux, 5 min, 94-95%; (**c**) (i) $TsOCH_2CH_2O(2\text{-}C_{10}H_7)$, K_2CO_3, DMF, 25 °C, 24 h; (ii) NH_4OH, 90% EtOH, reflux, 5 min, 61-78%.

It was also found that the treatment of 1,3-dibenzoyl-6-methyluracil (**3**) or 1,3-dibenzoyl-5,6-dimethyluracil (**4**) with an excess of anhydrous potassium carbonate in DMF for 24 h at room temperature in the absence of alkylating agent selectively results in 3-benzoyl-6-methyluracil (**12**) and 3-benzoyl-5,6-dimethyluracil (**13**) in the yields of 82% and 72%, respectively. These N^1-debenzoylation products were not previously described in the literature.

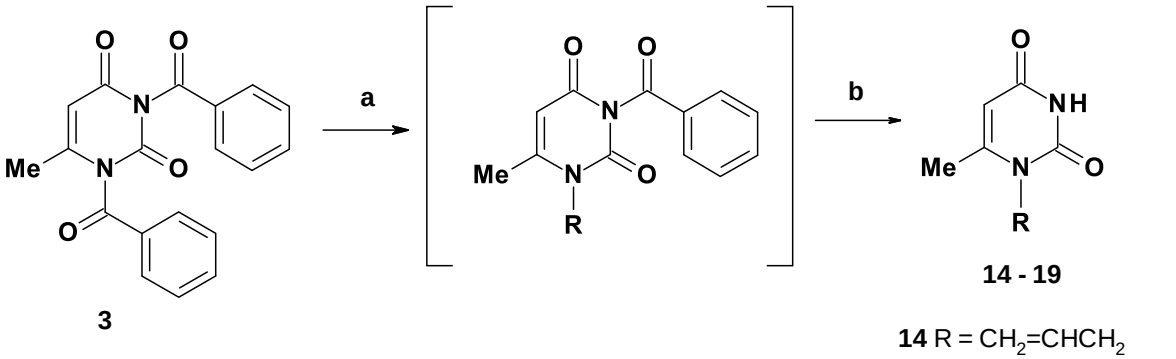
Compounds **7** and **8** were also prepared by alkylation of 3-benzoyluracils **12** and **13** by 2-(2-naphthyloxy)ethanol *p*-toluenesulfonate in the presence of potassium carbonate excess in anhydrous DMF at room temperature according to the method described above[32] followed by debenzoylation in

aqueous alcoholic solution of ammonia. This procedure did not give a significant increase in the overall yield of final products **7** and **8** to compare with a more convenient one-step synthesis described above.

Based on these results, we can conclude that primary products of 1,3-dibenzoyluracils (**1-3**) reaction with an excess of potassium carbonate in DMF are potassium salts of N^1-debenzoylation products, which subsequently form the 1-substituted 3-benzoyluracils (**9-11**).

Since the synthesis of 1-substituted uracils containing substituents at the 6-position of the pyrimidine cycle has the practical interest, the studies were done to evaluate the application of this method of 1,3-dibenzoyl-6-methyluracil (**3**) alkylation with different alkylating agents.

A number of alkylating agents were used for this purpose: allyl bromide, benzyl chloride, phenacyl bromide, 1-bromo-2-phenoxyethane, and *p*-toluenesulfonates of primary alcohols. As a result corresponding 1-substituted derivatives of 6-methyluracil **14-19** were synthesized with yields of 52-84% (Scheme 2). The use of α-methylbenzyl chloride as the alkylating agent did not lead to the desired N^1-alkylation products under different conditions (25 °C, 24 h or 80 °C, 2 h), and the only product was 3-benzoyl-6-methyluracil (**12**) isolated with the yield of 78-85%. It indicates a high sensitivity of the reaction to steric factors.



14 R = CH_2=$CHCH_2$
15 R = $PhCH_2$
16 R = $PhCH_2CH_2$
17 R = $PhOCH_2CH_2$
18 R = $PhCH_2OCH_2CH_2$
19 R = $PhC(O)CH_2$

Scheme 2. Reagents and conditions: (**a**) RX (X = Cl, Br, OTs), K_2CO_3, DMF, 25 °C, 24 h; (**b**) NH_4OH, 90% EtOH, reflux, 5 min, 52-84%.

Thus, 1,3-dibenzoyluracil, -thymine, -6-methyluracil and -5,6-dimethyluracil are convenient substrates to form potassium salts of N^1-debenzoylation products in anhydrous DMF in the presence of potassium carbonate at room temperature. These salts are capable of further *in situ* interacting with various alkylating agents. We have developed a method of synthesis, which allows to obtain N^1-monosubstituted 6-methyluracil derivatives in high yields and gives new synthetic possibilities in the field of pyrimidine compounds.

EXPERIMENTAL

All reagents were obtained at highest grade available from Sigma and Acros Organics and used without further purification unless otherwise noted. Anhydrous DMF and isopropanol were purchased from Sigma-Aldrich Co. Anhydrous acetone, 1,2-dichloroethane, and EtOAc were obtained by distillation over P_2O_5. NMR spectra were registered on a Bruker Avance 400 spectrometer (400 MHz for ^{1}H and 101.6 MHz for ^{13}C) in DMSO-d_6 with tetramethylsilane as an internal standard. High resolution mass spectra (HRMS) were registered on a Bruker Daltonics micrOTOF-Q II instrument using electrospray ionization (ESI). The measurements were acquired in a positive ion mode with the following parameters: interface capillary voltage 5000 V; mass range from *m/z* 50 to 3000; external calibration (Electrospray Calibrant Solution, Fluka); nebulizer pressure 0.4 Bar; flow rate 3 μL/min; nitrogen was applied as a dry gas (4 L/min); interface temperature was set at 190 °C. A sample of the compound in MeCN solution was injected into the mass spectrometer chamber from an Agilent 1260 HPLC system equipped with an Agilent Poroshell 120 EC-C18 (3.0 × 50 mm; 2.7 μm) column and a security guard, using an autosampler. The column was eluted in 80% MeCN (LC/MS grade) in water (bidistilled) with the flow rate of 200 μL/min. TLC was performed on Merck TLC Silica gel 60 F_{254} plates eluted with (a) EtOAc or (b) EtOAc/1,2-dichloroethane (1:1) and detected with UV-lamp VL-6.LC (France). Melting points were determined in glass capillaries on a Mel-Temp 3.0 (Laboratory Devices Inc., USA). Yields refer to spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials.

1,3-Dibenzoyluracil (**1**) and 1,3-dibenzoylthymine (**2**) were prepared according to the previously described method.[31]

1,3-Dibenzoyl-6-methyluracil (3). To a suspension of 6-methyluracil (5.0 g, 0.040 mol) in anhydrous MeCN (100 mL) and anhydrous pyridine (20 mL) benzoyl chloride (12.5 mL, 0.108 mol) was added in one portion and stirred at room temperature for 24 h. The reaction mixture was concentrated *in vacuo* at a bath temperature not exceeding 60 °C, cooled and the residue partitioned between $CHCl_3$ (200 mL) and ice water (100 mL). The organic phase was separated, dried over sodium sulfate, filtered and evaporated *in vacuo* at a bath temperature not exceeding 60 °C. The residue was crystallized from Et_2O (25 mL) to give 10.0 g (76%) of compound **3** as a yellow crystalline solid with mp 80-82 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.59 (3H, s, CH_3), 7.55 (1H, s, H^5), 7.58-7.65 (4H, m, aryl), 7.74-7.81 (2H, m, aryl), 8.10-8.16 (4H, m, aryl). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 26.97, 114.88, 130.87, 130.93, 132.59, 132.61, 133.37, 133.51, 138.21, 138.30, 163.42, 166.30, 167.03, 170.17, 177.57.

1,3-Dibenzoyl-5,6-dimethyluracil (**4**) was synthesized similarly but was isolated as an oil and used in the next step without further purification.

3-Benzoyl-6-methyluracil (12). A mixture of 1,3-dibenzoyl-6-methyluracil (**3**) (2.0 g, 5.98 mmol) and finely ground anhydrous potassium carbonate (2.0 g, 14.47 mmol) was stirred in anhydrous DMF (40

mL) at room temperature for 24 h, filtered, and the filtrate was evaporated *in vacuo*, cooled and the residue partitioned between $CHCl_3$ (50 mL) and water (50 mL). The aqueous phase was separated, acidified to pH 2, kept for 1 h at 0-5 °C, the precipitate was filtered off, washed on the filter with cold water (2 × 5 mL), and air dried to give 1.30 g (94 %) of the crude product as a pearlescent flake crystals, mp 205.5-208.5 °C. Recrystallization from EtOAc (100 mL) gave 1.13 g (82%) of light yellow crystalline solid, mp 218-221 °C, R_f 0.27 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.13 (3H, s, CH_3), 5.62 (1H, s, H^5), 7.55-7.62 (2H, m, aryl), 7.72-7.79 (1H, m, aryl), 7.91-7.97 (2H, m, aryl), 11.59 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 18.82, 98.83, 129.77, 130.49, 131.81, 135.63, 150.30, 154.71, 162.88, 170.50. ESI-HRMS: $C_{12}H_{10}N_2O_3$: calcd for $[M + H]^+$ 231.0764, found *m*/*z* 231.0766; calcd for $[M + Na]^+$ 253.0584, found *m*/*z* 253.0586; calcd for $[2M + H]^+$ 461.1456, found *m*/*z* 461.1465; calcd for $[2M + Na]^+$ 483.1275, found *m*/*z* 483.1279.

3-Benzoyl-5,6-dimethyluracil (13) was prepared analogously and obtained as pale yellow crystals, yield 72%, mp 228-231 °C, R_f 0.61 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 1.79 (3H, s, CH_3), 2.15 (3H, s, CH_3), 7.56-7.62 (2H, m, aryl), 7.73-7.79 (1H, m, aryl), 7.91-7.95 (2H, m, aryl), 11.39 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 9.84, 16.86, 104.63, 129.77, 130.50, 131.80, 135.60, 149.37, 149.52, 163.50, 170.51. ESI-HRMS: $C_{13}H_{12}N_2O_3$: calcd for $[M + H]^+$ 245.0921, found *m*/*z* 245.0924; calcd for $[M + Na]^+$ 267.0740, found *m*/*z* 267.0744; calcd for $[2M + NH_4]^+$ 506.2034, found *m*/*z* 506.2044; calcd for $[2M + Na]^+$ 511.1588, found *m*/*z* 511.1596.

General procedure for the synthesis of 1-substituted uracil derivatives 5-8 and 14-19. A mixture of 1,3-dibenzoyluracil derivative **1-4** (5.98 mmol), the alkylating agent (5.84 mmol) and finely ground anhydrous potassium carbonate (2.0 g, 14.47 mmol) were stirred in anhydrous DMF (40 mL) for 24 h at room temperature. The reaction mixture was filtered, the precipitate was washed on the filter with DMF (5 × 2 mL), the filtrate was evaporated *in vacuo* and the residue partitioned between $CHCl_3$ (100 mL) and water (50 mL), the organic phase was separated, dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was dissolved in 95% EtOH (25 mL), treated with conc. aqueous ammonium hydroxide (2.5 mL), boiled for 5 min, and kept at 0-5 °C within a day. The precipitate was filtered, washed on the filter with cold 95% EtOH (5 mL), Et_2O (5 mL), hexane (10 mL), air dried and crystallized from 95% EtOH.

1-[2-(2-Naphthyloxy)ethyl]uracil (5). Yield 71%, mp 211-213 °C, R_f 0.39 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 4.13 (2H, t, J = 5 Hz, CH_2), 4.29 (2H, t, J = 5 Hz, CH_2), 5.59 (1H, d, J = 8 Hz, H^5), 7.11-7.47 (4H, m, aryl), 7.72 (1H, d, J = 8 Hz, H^6), 7.78-7.83 (3H, m, aryl), 11.36 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 50.30, 68.65, 104.05, 110.34, 121.84, 127.13, 129.84, 130.10, 130.89, 131.99, 132.79, 137.55, 149.73, 154.39, 159.23, 167.14. ESI-HRMS: $C_{16}H_{14}N_2O_3$: calcd for $[M + H]^+$ 283.1077, found *m*/*z* 283.1079; calcd for $[M + Na]^+$ 305.0897, found *m*/*z* 305.0895; calcd for $[2M + H]^+$

565.2082, found *m*/*z* 565.2084; calcd for $[2M + Na]^+$ 587.1901, found *m*/*z* 587.1901.

1-[2-(2-Naphthyloxy)ethyl]thymine (6). Yield 78%, mp 212-215 °C, R_f 0.32 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 1.76 (3H, s, CH_3), 4.08 (2H, t, J = 5 Hz, CH_2), 4.28 (2H, t, J = 5 Hz, CH_2), 7.12-7.47 (4H, m, aryl), 7.60 (1H, s, H^6), 7.76-7.83 (3H, m, aryl), 11.33 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 15.32, 50.02, 68.69, 110.35, 111.61, 121.88, 127.12, 129.83, 130.09, 130.89, 131.98, 132.78, 137.55, 145.40, 154.35, 159.26, 167.68. ESI-HRMS: $C_{17}H_{16}N_2O_3$: calcd for $[M + H]^+$ 297.1234, found *m*/*z* 297.1227; calcd for $[M + Na]^+$ 319.1053, found *m*/*z* 319.1049; calcd for $[2M + H]^+$ 593.2395, found *m*/*z* 593.2391; calcd for $[2M + Na]^+$ 615.2214, found *m*/*z* 615.2210.

1-[2-(2-Naphthyloxy)ethyl]-6-methyluracil (7). Yield 73%, mp 216.5-218.5 °C, R_f 0.24 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.35 (3H, s, CH_3), 4.17 (2H, t, J = 5 Hz, CH_2), 4.29 (2H, t, J = 5 Hz, CH_2), 5.52 (1H, s, H^5), 7.11-7.46 (4H, m, aryl), 7.75-7.83 (3H, m, aryl), 11.27 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 23.11, 46.45, 68.68, 104.51, 110.20, 121.75, 127.13, 129.85, 130.10, 130.90, 131.98, 132.81, 137.56, 155.01, 158.11, 159.25, 165.88. ESI-HRMS: $C_{17}H_{16}N_2O_3$: calcd for $[M + H]^+$ 297.1234, found *m*/*z* 297.1225; calcd for $[M + Na]^+$ 319.1053, found *m*/*z* 319.1046; calcd for $[2M + H]^+$ 593.2395, found *m*/*z* 593.2383; calcd for $[2M + Na]^+$ 615.2214, found *m*/*z* 615.2205.

1-[2-(2-Naphthyloxy)ethyl]-5,6-dimethyluracil (8). Yield 61%, mp 202-204 °C, R_f 0.45 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 1.83 (3H, s, CH_3), 2.36 (3H, s, CH_3), 4.23 (2H, t, J = 5 Hz, CH_2), 4.28 (2H, t, J = 6 Hz, CH_2), 7.11-7.48 (4H, m, aryl), 7.76-7.84 (3H, m, aryl), 11.33 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 11.29, 16.78, 43.57, 65.79, 106.58, 107.11, 118.76, 124.06, 126.79, 127.04, 127.84, 128.90, 129.72, 134.51, 149.82, 151.30, 156.21, 163.53. ESI-HRMS: $C_{18}H_{18}N_2O_3$: calcd for $[M + H]^+$ 311.1390, found *m*/*z* 311.1384; calcd for $[M + Na]^+$ 333.1210, found *m*/*z* 333.1206; calcd for $[2M + H]^+$ 621.2708, found *m*/*z* 627.2702; calcd for $[2M + Na]^+$ 643.2527, found *m*/*z* 643.2523.

1-Allyl-6-methyluracil (14). Yield 52%, mp 171.5-173 °C, R_f 0.27 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.18 (3H, s, CH_3), 4.38-4.41 (2H, m, CH_2), 4.98-5.17 (2H, m, $=CH_2$), 5.51 (1H, s, H^5), 5.83-5.94 (1H, m, =CH), 11.22 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 19.17, 45.34, 101.36, 115.98, 133.57, 151.70, 154.61, 162.83. ESI-HRMS: $C_8H_{10}N_2O_2$: calcd for $[M + H]^+$ 167.0815, found *m*/*z* 167.0805; calcd for $[M + Na]^+$ 189.0634, found *m*/*z* 189.0632; calcd for $[2M + Na]^+$ 355.1377, found *m*/*z* 355.1399.

1-Bezyl-6-methyluracil (15). Yield 84%, mp 236-238 °C, R_f 0.29 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.11 (3H, s, CH_3), 5.04 (2H, s, CH_2), 5.56 (1H, s, H^5), 7.15-7.38 (5H, m, aryl), 11.36 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 19.55, 46.28, 101.75, 126.25, 127.58, 129.12, 137.38, 152.34, 154.65, 162.82. ESI-HRMS: $C_{12}H_{12}N_2O_2$: calcd for $[M + H]^+$ 217.0972, found *m*/*z* 217.0972; calcd for $[M + Na]^+$ 239.0791, found *m*/*z* 239.0797; calcd for $[2M + H]^+$ 433.1870, found *m*/*z* 433.1876; calcd for $[2M + Na]^+$ 455.1690, found *m*/*z* 455.1694.

1-(2-Phenylethyl)-6-methyluracil (16). Yield 59%, mp 205-208 ºC, R_f 0.30 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.09 (3H, s, CH_3), 2.86 (2H, t, J = 8 Hz, CH_2), 3.89 (2H, t, J = 8 Hz, CH_2), 5.43 (1H, s, H^5), 7.20-7.34 (5H, m, aryl), 11.23 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 19.39, 34.31, 45.35, 101.21, 126.89, 128.86, 129.17, 138.56, 151.76, 154.56, 162.81. ESI-HRMS: $C_{13}H_{14}N_2O_2$: calcd for $[M + H]^+$ 231.1128, found *m*/*z* 231.1129; calcd for $[M + Na]^+$ 253.0947, found *m*/*z* 253.0950; calcd for $[2M + H]^+$ 461.2183, found *m*/*z* 461.2190; calcd for $[2M + Na]^+$ 483.2003, found *m*/*z* 483.2007.

1-(2-Phenoxyethyl)-6-methyluracil (17). Yield 69%, mp 186-189 ºC, R_f 0.27 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.32 (3H, s, CH_3), 4.10 (2H, t, J = 5 Hz, CH_2), 4.16 (2H, t, J = 5 Hz, CH_2), 5.51 (1H, s, H^5), 6.91-6.96 (3H, m, aryl), 7.24-7.30 (2H, m, aryl), 11.26 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 20.02, 43.43, 65.34, 101.41, 114.61, 121.27, 129.91, 151.91, 155.07, 158.31, 162.84. ESI-HRMS: $C_{13}H_{14}N_2O_3$: calcd for $[M + H]^+$ 247.1077, found *m*/*z* 247.1080; calcd for $[M + Na]^+$ 269.0897, found *m*/*z* 269.0901; calcd for $[2M + H]^+$ 493.2082, found *m*/*z* 493.2089; calcd for $[2M + Na]^+$ 515.1901, found *m*/*z* 515.1909.

1-(2-Benzyloxyethyl)-6-methyluracil (18). Yield 67%, mp 145-147 ºC, R_f 0.29 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.26 (3H, s, CH_3), 3.60 (2H, t, J = 5 Hz, CH_2), 3.93 (2H, t, J = 5 Hz, CH_2), 4,47 (2H, s, CH_2), 5.49 (1H, s, H^5), 7.22-7.34 (5H, aryl), 11.20 c (1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 20.07, 43.85, 67.63, 72.38, 101.19, 127.48, 127.78, 128.59, 138.49, 151.80, 155.23, 162.89. ESI-HRMS: $C_{14}H_{16}N_2O_3$: calcd for $[M + H]^+$ 261.1234, found *m*/*z* 261.1235; calcd for $[M + Na]^+$ 283.1053, found *m*/*z* 283.1054; calcd for $[2M + H]^+$ 521.2395, found *m*/*z* 521.2403; calcd for $[2M + Na]^+$ 543.2221, found *m*/*z* 543.2214.

1-(2-Phenyl-2-oxoethyl)-6-methyluracil (19). Yield 54%, mp 252-255 ºC, R_f 0.28 (a). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.09 (3H, s, CH_3), 5.42 (2H, s, CH_2), 5.59 (1H, s, H^5), 7.56-7.62 (2H, m, aryl), 7.70-7.75 (1H, m, aryl), 8.04-8.08 (2H, m, aryl), 11.35 (1H, s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 19.61, 50.43, 101.27, 128.46, 129.29, 134.44, 134.58, 151.99, 154.76, 162.90, 194.01. ESI-HRMS: $C_{13}H_{12}N_2O_3$: calcd for $[M + H]^+$ 245.0921, found *m*/*z* 245.0921; calcd for $[M + Na]^+$ 267.0740, found *m*/*z* 267.0746; calcd for $[2M + H]^+$ 489.1769, found *m*/*z* 489.1772; calcd for $[2M + Na]^+$ 511.1588, found *m*/*z* 511.1592.

General procedure for the synthesis of 1-[2-(2-naphthyloxy)ethyl]-3-benzoyluracil derivatives 9-11. A mixture of 1,3-dibenzoyluracil derivative **1-3** (5.98 mmol), *p*-toluenesulfonate of 2-(2-naphthyloxy)ethanol (2.0 g, 5.84 mmol) and finely ground anhydrous potassium carbonate (2.0 g, 14.47 mmol) were stirred in anhydrous DMF (40 mL) for 24 h at room temperature. The reaction mixture was filtered, the precipitate on the filter was washed with DMF (5 × 2 mL), the filtrate was evaporated *in vacuo*, the residue partitioned between $CHCl_3$ (100 mL) and water (50 mL). The organic phase was separated, dried over sodium sulfate, filtered and evaporated *in vacuo*. The resulting oil was triturated

with Et_2O (20 mL), kept at 0-5 °C within a day, the crystallized product was filtered, washed on the filter with Et_2O (5 mL) and hexane (10 mL), air dried and crystallized from acetone.

1-[2-(2-Naphthyloxy)ethyl]-3-benzoyluracil (9). Yield 77%, mp 171-173.5 °C, R_f 0.73 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 4.25 (2H, t, J = 5 Hz, CH_2), 4.38 (2H, t, J = 5 Hz, CH_2), 5.91 (1H, d, J = 8 Hz, H^5), 7.17-7.56 (6H, m, aryl), 7.71-7.96 (6H, m, aryl), 8.01 (1H, d, J = 8 Hz, H^6). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 47.80, 65.55, 100.83, 107.48, 118.81, 124.16, 126.84, 127.09, 127.89, 129.03, 129.80, 130.57, 131.46, 134.52, 135.80, 147.60, 150.01, 156.23, 162.65, 169.95. ESI-HRMS: $C_{23}H_{18}N_2O_4$: calcd for $[M + H]^+$ 387.1339, found m/z 387.1329; calcd for $[M + Na]^+$ 409.1159, found m/z 409.1148; calcd for $[2M + H]^+$ 773.2606, found m/z 776.2597; calcd for $[2M + Na]^+$ 795.2425, found m/z 795.2419.

1-[2-(2-Naphthyloxy)ethyl]-3-benzoylthymine (10). Yield 67%, mp 168-170.5 °C, R_f 0.78 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 1.87 (3H, s, CH_3), 4.20 (2H, t, J = 5 Hz, CH_2), 4.38 (2H, t, J = 5 Hz, CH_2), 7.16-7.56 (6H, m, aryl), 7.72-7.92 (6H, m, aryl), 7.89 (1H, s, H^6). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 12.16, 47.51, 65.58, 107.50, 108.72, 118.84, 124.14, 126.83, 127.06, 127.87, 129.00, 129.78, 130.56, 131.51, 134.51, 135.74, 143.24, 149.88, 156.25, 163.21, 170.02. ESI-HRMS: $C_{24}H_{20}N_2O_4$: calcd for $[M + H]^+$ 401.1496, found m/z 401.1491; calcd for $[M + Na]^+$ 423.1315, found m/z 423.1311; calcd for $[2M + NH_4]^+$ 818.3184, found m/z 818.3189; calcd for $[2M + Na]^+$ 823.2738, found m/z 823.2743.

1-[2-(2-Naphthyloxy)ethyl]-3-benzoyl-6-methyluracil (11). Yield 54%, mp 173.5-175.5 °C, R_f 0.71 (b). ^{1}H NMR (400 MHz, DMSO-d_6), δ ppm 2.49 (3H, s, CH_3), 4.27 (2H, t, J = 5 Hz, CH_2), 4.35 (2H, t, J = 5 Hz, CH_2), 5.84 (1H, s, H^5), 7.13-7.55 (6H, m, aryl), 7.70-7.92 (6H, m, aryl). ^{13}C NMR (100 MHz, DMSO-d_6), δ ppm 23.37, 47.14, 68.62, 104.13, 110.35, 121.77, 127.19, 129.89, 130.13, 130.92, 132.03, 132.82, 132.86, 133.59, 134.57, 137.56, 138.80, 153.57, 159.28, 159.66, 164.37, 172.95. ESI-HRMS: $C_{24}H_{20}N_2O_4$: calcd for $[M + H]^+$ 401.1496, found m/z 401.1496; calcd for $[M + Na]^+$ 423.1315, found m/z 423.1316; calcd for $[2M + H]^+$ 801.2919, found m/z 801.2929; calcd for $[2M + Na]^+$ 823.2738, found m/z 823.2753.

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