# Practical synthesis of some novel unsymmetrical 1,3-dialkyl pyrimidine derivatives at room temperature

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**Abstract**

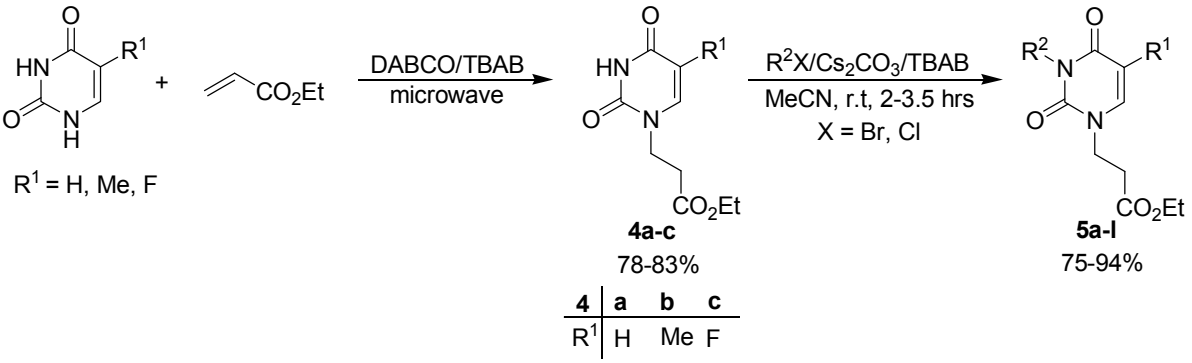
The efficient synthesis of some novel unsymmetrical 1,3-dialkylpyrimidines is described. *N*3-Alkylation of *N*1-substituted pyrimidine derivatives with various functionalized alkyl halides in the presence of catalytic amount of tetrabutylammonium bromide (TBAB) and $Cs_2CO_3$ in MeCN affords the title compounds. The reactions proceed at room temperature and the products are obtained in good to excellent yields.

**Keywords:** 1,3-Dialkylpyrimidine, nucleobase, *N*3-alkylation, alkyl halide

## Introduction

In recent years, there has been a growing interest in the synthesis of bioactive compounds in organic chemistry.[1] One important class of these compounds is modified *N*-substituted nucleobases, including acyclic,[2] carboacyclic,[3] carbocyclic,[4] aza[5] and thionucleosides.[6] Some nucleoside derivatives possessing pyrimidine nucleobases have biological activities. The *N*1-β-hydroxy alkyl pyrimidine nucleobases seem to have attractive structures for investigation of carcinogenesis[3a] and as accesses to therapeutic agents such as antiviral pyrimidine derivatives.[3b] Furthermore, the *N*1,*N*3-disubstituted pyrimidines are interesting as these compounds have required scaffold to consider as intercalating and alkylating agents.[7] The intercalating and alkylating agents nowadays have critical role in cancer chemotherapy.[7] Antiviral activity has been also reported for these compounds.[8] 1,3-Dialkylpyrimidine derivatives are prepared by *N*3-alkylation of 1-alkylpyrimidines[9] or *N*1,*N*3-dialkylation of pyrimidine nucleobases.[10] For this purpose, several bases, such as sodium hydride,[9a] tetrabutylammonium fluoride (TBAF),[9b] potassium fluoride,[9c] potassium carbonate,[9d] magnesium oxide[10a] and potassium hydroxide[10b] have been used. These methods are often associated with one or more of the following

drawbacks: (i) the use of DMF as solvent with cumbersome workup of the reaction mixture;[9a,9d] (ii) long reaction times;[9b,9d] (iii) low yields;[9d,10] and (iv) harsh conditions in which the use of low boiling point alkylating agent is difficult.[9c-d,10a] To overcome these drawbacks and also in extension of our previous studies on synthesis of nucleoside derivatives,[10a,11] we describe here a practical, simple and efficient synthesis of some novel unsymmetrical 1,3-dialkylpyrimidine derivatives via *N*3-alkylation of 1-alkylpyrimidines with carbon electrophiles in the presence of catalytic amount of TBAB and $Cs_2CO_3$ in MeCN at room temperature (Scheme 1). In these mild conditions, alkylating agents with low boiling point, such as allyl bromide and propargyl chloride can be easily employed.




| 5 | $R^1$ | $R^2$ | 5 | $R^1$ | $R^2$ | 5 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|
| **a** | H | Cl | **e** | H | OH | **i** | Me | Cl |
| **b** | H | NPht | **f** | H | $NO_2$ | **j** | Me | OH |
| **c** | H | $(CH_2)_3$NPht | **g** | H | | **k** | F | Cl |
| **d** | H | $CO_2Et$ | **h** | H | | **l** | F | OH |

NPht = Phthalimide

**Scheme 1.** Synthesis of *N*1,*N*3-dialkylated pyrimidines.

## Results and Discussion

In order to optimize the reaction conditions, the reaction of carboacyclic nucleoside **4a** with 1-bromo-3-chloropropane was studied as a model reaction to provide compound **5a**. At first, the influence of various bases in the presence of catalytic amounts of TBAB was examined to evaluate their capabilities (Table 1). Higher yields and shorter reaction times were observed when $Cs_2CO_3$ was used as base. Therefore, $Cs_2CO_3$ was the base of choice for all reactions.

Several reactions were carried out to understand the effect of other solvents beside MeCN on the results of reaction. A set of anhydrous solvents was examined for the previously described

model reaction. The results are depicted in Table 2. As Table 2 indicates, the best results were obtained with MeCN.

To compare the efficiency of solution conditions versus solvent-free conditions, we have examined the model reaction under solvent-free conditions (microwave and thermal). The results are summarized in Table 3. As it is clear from Table 3, the solution conditions are more efficient.

**Table 1.** The influence of bases (0.010 mol) on reaction of compound **4a** (0.010 mol) with 1-bromo-3-chloropropane (0.015 mol) in the presence of TBAB (0.001 mol) in MeCN (30 mL) at room temperature

| *Entry* | *Base* | *Time (h)* | *Yield[a] (%)* |
|---|---|---|---|
| 1 | $Cs_2CO_3$ | 2 | 94 |
| 2 | $CsHCO_3$ | 6 | 42 |
| 3 | CsOH | 4 | 30 |
| 4 | NaOH | 6 | 26 |
| 5 | $K_2CO_3$ | 6 | 69 |
| 6 | MgO | 6 | trace |
| 7 | CaO | 6 | trace |
| 8 | *t*-BuOK | 6 | 33 |
| 9 | DABCO | 6 | 9 |

[a]Isolated yield

**Table 2.** The effect of solvents on reaction in the presence of TBAB and $Cs_2CO_3$ at room temperature

| *Entry* | *Solvent* | *Time (h)* | *Yield[a] (%)* |
|---|---|---|---|
| 1 | MeCN | 2 | 94 |
| 2 | Acetone | 2 | 92 |
| 3 | $CH_2Cl_2$ | 2 | 91 |
| 4 | $CHCl_3$ | 4 | 77 |
| 5 | THF | 2 | 88 |
| 6 | DMF | 2 | 90 |
| 7 | DMSO | 3 | 87 |
| 8 | Toluene | 4 | 41 |
| 9 | Benzene | 4 | 37 |

[a]Isolated yield

**Table 3.** Comparative reaction of compound **4a** (0.010 mol) with 1-bromo-3-chloropropane (0.015 mol) in the presence of TBAB (0.001 mol) and $Cs_2CO_3$ (0.010 mol) using solvent-free (microwave, 300 W; thermal, 100 °C) versus the solution conditions (MeCN, 30 mL, r.t)

| *Conditions* | *Time (min)* | *Yield[a] (%)* |
|---|---|---|
| Solution | 120 | 94 |
| Microwave | 6 | 80 |
| Thermal | 120 | 73 |

[a]Isolated yield

To investigate the versatility as well as the capacity of our method, the reactions were examined with various *N*1-substituted nucleobases and alkyl halides (Table 4). As it is shown in Table 4, the reactions proceeded efficiently and the desired *N*1,*N*3-dialkylated pyrimidines were obtained in good to excellent yields.

The effect of substituents (Me and F) on 5-position of 1-alkyl pyrimidines on *N*3-alkylation reaction was also studied. As Table 4 shows, the presence of a fluoro substituent had no significant effect on the reaction but the presence of a methyl substituent lowered the yields and increased the reaction times (Table 4, entries 9-12). Compound **5d** was obtained via reaction of carboacyclic nucleoside **4a** with ethyl 3-bromopropanoate as well as ethyl acrylate. As Table 4 indicates, the reaction yield was remarkably higher when alkyl halide was used rather than α,β-unsaturated ester (Table 4, entries 4 and 15). *N*3-Alkylation of carboacyclic nucleoside **4a** with epoxide in the presence of TBAB and $Cs_2CO_3$ in MeCN at room temperature was not successful (Table 4, entry 16).

This method can be easily applied for *N*3-alkylation of 5'-protected uridine (classic nucleoside) (Table 4, entries 13-14). The 5'-DMT-uridine **6** reacted with 1-bromo-3-chloropropane and 2-(4-bromo-butyl)-isoindole-1,3-dione to afford compounds **7a** and **7b** in excellent yields and reasonable times (Table 4, entries 13-14). The sugar residue has a little effect on *N*3-alkylation of uracil, nevertheless, it was expected that bulky sugar moiety to decrease the *N*3 tendency for alkylation.

**Table 4.** *N*3-Alkylation of *N*1-substituted pyrimidine nucleobases with different alkylating agent in the presence of TBAB and $Cs_2CO_3$ in MeCN at room temperature

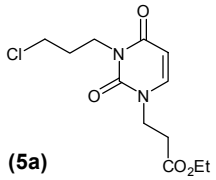
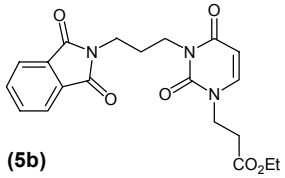
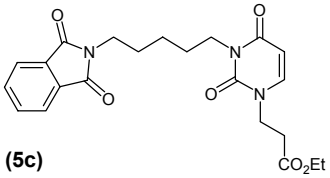
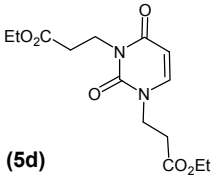
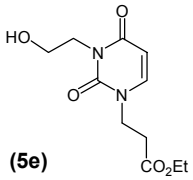
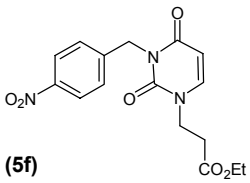
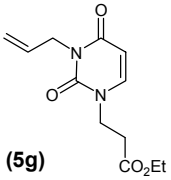
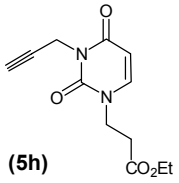
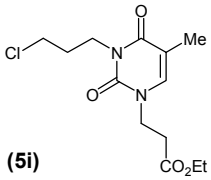
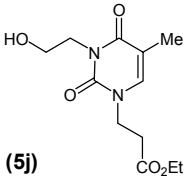
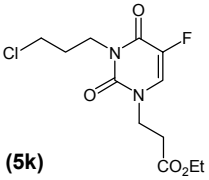
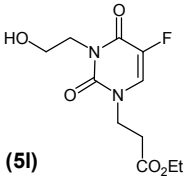
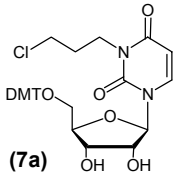
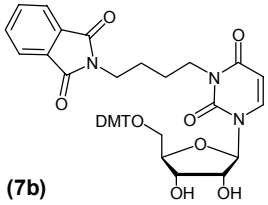
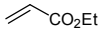
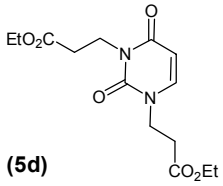
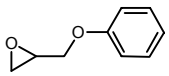
| Entry | Alkylating Agent | Product | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 1 | RBr |  **(5a)** | 2 | 94 |
| 2 | RBr |  **(5b)** | 3 | 93 |
| 3 | RBr |  **(5c)** | 3 | 91 |
| 4 | RBr |  **(5d)** | 2.5 | 88 |
| 5 | RBr |  **(5e)** | 3 | 76 |
| 6 | RBr |  **(5f)** | 2.5 | 82 |
| 7 | RBr |  **(5g)** | 2 | 90 |
| 8 | RCl |  **(5h)** | 2 | 86 |

**Table 4.** *N*3-Alkylation of *N*1-substituted pyrimidine nucleobases with different alkylating agent in the presence of TBAB and $Cs_2CO_3$ in MeCN at room temperature (continued)

| Entry | Alkylating Agent | Product | Time (h) | Yield[a] (%) |
|---|---|---|---|---|
| 9 | RBr |  **(5i)** | 3 | 79 |
| 10 | RBr |  **(5j)** | 3.5 | 62 |
| 11 | RBr |  **(5k)** | 2 | 93 |
| 12 | RBr |  **(5l)** | 3 | 75 |
| 13 | RBr |  **(7a)** | 12 | 88 |
| 14 | RBr |  **(7b)** | 14 | 87 |
| 15 |  |  **(5d)** | 3 | 26 |
| 16[b] |  | - | 12 | - |

[a]Isolated yield. [b]No reaction was observed even by changing the solvent.

## Conclusions

In summary, we have developed an efficient and simple method for *N*3-alkylation of *N*1-alkylpyrimine nucleobases in mild conditions. In this method, 1,3-dialkylpyrimidine nucleobases were synthesized as biologically interesting compounds in good to excellent yields.

## Experimental Section

**General Procedures.** All chemicals were prepared from Merck or Fluka chemical companies. Solvents were purified and dried according to reported methods and stored over molecular sieves 0.3 nm.[12] The progress of reaction was followed with TLC using silica gel SILG/UV 254 plates. Silica gel 60, 0.063-0.200 mm (70-230 mesh ASTM) was used for column chromatography. IR spectra were run on a Shimadzu FTIR-8300 spectrophotometer. The $^{1}$H NMR (250 MHz) and $^{13}$C NMR (62.5 MHz) were run on a Bruker Avanced DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a Perkin–Elmer 240-B microanalyzer.

***N*3-Alkylation of *N*1-substituted Pyrimidines with Carbon Electrophiles.** A mixture of compounds consisting of 1-alkylpyrimidine nucleobase (0.010 mol), alkylating agent (0.015 mol), TBAB (0.322 g, 0.001 mol) and $Cs_2CO_3$ (3.258 g, 0.010 mol) in anhydrous MeCN (30 mL) was stirred at room temperature for appropriate time (Table 3). Then, the solids were filtered off and washed with MeCN (20 mL). The filtrate and washings were combined, the solvent was evaporated and the residual product was purified by column chromatography on silica gel with EtOAc/*n*-hexane (1/1).

**3-(2,4-Dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)-propionic acid ethyl ester (4a).** Colourless crystals; yield: 83%; mp 78-80 °C (Lit.[11a] mp 78-80 °C).

**3-(5-Methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)-propionic acid ethyl ester (4b)**. Colourless crystals; yield: 78%; mp 148-149 °C (Lit.[11a] mp 148-149 °C).

**3-(5-Fluoro-2,4-dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl)-propionic acid ethyl ester (4c).** Pale yellow crystals; yield: 81%; mp 122-124 °C (Lit.[11a] mp 122-124 °C).

**3-[3-(3-Chloro-propyl)-2,4-dioxo-3,4-dihydro-2*H*- pyrimidin-1-yl] propionic acid ethyl ester (5a).** Pale yellow oil; isolated yield: 2.71 g (94%); IR (neat) $\nu_{max}$ (cm$^{-1}$): 3055, 2965, 1734, 1705, 1635; $^{1}$H NMR ($CDCl_3$): δ 1.14 (3H, t, *J* = 7.1 Hz, $CH_2\mathit{CH_3}$), 1.98 (2H, m, $ClCH_2\mathit{CH_2}$), 2.65 (2H, t, *J* = 5.9 Hz, O=C$\mathit{CH_2}$), 3.45 (2H, t, *J* = 7.4 Hz, $ClCH_2CH_2\mathit{CH_2}$), 3.87-4.03 (6H, complex, Cl$\mathit{CH_2}$, O=C$CH_2\mathit{CH_2}$ and $CH_3\mathit{CH_2}$), 5.57 (1H, d, *J* = 8.0 Hz, $H_5$ of uracil), 7.27 (1H, d, *J* = 8.0 Hz, $H_6$ of uracil); $^{13}$C NMR ($CDCl_3$): δ 14.4, 30.9, 33.2, 39.2, 42.9, 46.4, 61.3, 101.3, 144.1, 151.6, 163.2, 171.6; MS m/z (%): 289 ($M^+$+1, 15), 288 ($M^+$, 2), 253 (61), 226 (25), 207 (26), 153 (32), 97 (52), 82 (84), 55 (100); Anal. calcd for $C_{12}H_{17}ClN_2O_4$: C, 49.92; H, 5.93; N, 9.70. Found: C, 50.21; H, 6.10; N. 9.46.

**3-{3-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl}- propionic acid ethyl ester (5b).** Colourless crystals; mp 130-132 °C; isolated yield: 3.70 g (93%); IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3042, 2949, 1771, 1723, 1701, 1662; $^1$H NMR ($CDCl_3$): δ 1.19 (3H, t, *J* = 7.2 Hz, $CH_2CH_3$), 2.02 (2H, m), 2.73 (2H, t, *J* = 6.0 Hz, O=C$CH_2$), 3.72 (2H, t, *J* = 7.0 Hz), 3.92-4.01 (4H, complex), 4.09 (2H, q, *J* = 7.2 Hz, $CH_3CH_2$), 5.64 (1H, d, *J* = 8.0 Hz, $H_5$ of uracil), 7.31(1H, d, *J* = 8.0 Hz, $H_6$ of uracil), 7.67 (2H, m), 7.81 (2H, m); $^{13}$C NMR ($CDCl_3$): δ 13.1, 25.8, 31.9, 34.8, 37.8, 45.1, 60.1, 100.2, 122.2, 131.1, 132.9, 142.6, 150.3, 161.9, 167.3, 170.4; MS m/z (%): 400 ($M^+$+1, 4), 399 ($M^+$, 10), 354 (12), 299 (8), 239 (22), 226 (100), 193 (31), 152 (68), 96 (60), 82 (82), 55 (85); Anal. calcd for $C_{20}H_{21}N_3O_6$: C, 60.14; H, 5.30; N, 10.52. Found: C, 59.95; H, 5.58; N. 10.73.

**3-{3-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentyl]-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl}- propionic acid ethyl ester (5c).** Colourless crystals; mp 125-127 °C; isolated yield: 3.88 g (91%); IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3057, 2961, 1772, 1725, 1701, 1665; $^1$H NMR ($CDCl_3$): δ = 1.15 (3H, t, *J* = 7.0 Hz, $CH_2CH_3$), 1.33 (2H, m), 1.55-1.66 (4H, complex), 2.69 (2H, t, *J* = 5.9 Hz, O=C$CH_2$), 3.60 (2H, t, *J* = 6.9 Hz,), 3.79-3.90 (4H, complex), 4.08 (2H, q, *J* = 7.0 Hz, $CH_3CH_2$), 5.56 (1H, d, *J* = 7.9 Hz, $H_5$ of uracil), 7.26 (1H, d, *J* = 7.9 Hz, $H_6$ of uracil), 7.64 (2H, m), 7.75 (2H, m); $^{13}$C NMR ($CDCl_3$): δ 14.5, 24.5, 27.4, 28.6, 33.4, 38.1, 41.2, 46.5, 61.4, 101.6, 123.5, 132.5, 134.2, 143.7, 151.7, 163.3, 168.7, 171.7; MS m/z (%): 428 ($M^+$+1, 4), 427 ($M^+$, 8), 382 (8), 267 (28), 213 (59), 160 (72), 113 (63), 97 (55), 82 (85), 554 (100); Anal. calcd for $C_{22}H_{25}N_3O_6$: C, 61.82; H, 5.90; N, 9.83. Found: C, 62.15; H, 5.66; N. 9.99.

**3-[3-(2-Ethoxycarbonyl-ethyl)-2,4-dioxo-3,4-dihydro-2*H*-pyrimidine-1-yl]-propionic acid ethyl ester (5d).** Pale yellow oil; isolated yield: 2.75 g (88 %); IR (neat) $\nu_{max}$ ($cm^{-1}$): 3044, 2981, 1732, 1705, 1666; $^1$H NMR ($CDCl_3$): δ 1.13 (6H, t, *J* = 7.1 Hz, $2CH_2CH_3$), 2.49 (2H, t, *J* = 7.5 Hz), 2.65 (2H, t, *J* = 6.0 Hz), 3.89 (2H, t, *J* = 6.0 Hz,), 3.95-4.08 (6H, complex), 5.57 (1H, d, *J* = 7.9 Hz, $H_5$ of uracil), 7.28 (1H, d, *J* = 7.9 Hz, $H_6$ of uracil); $^{13}$C NMR ($CDCl_3$): δ 14.4, 32.4, 33.2, 37.1, 46.4, 60.8, 61.3, 101.3, 144.1, 151.4, 163.0, 171.3, 171.6; MS m/z (%): 313 ($M^+$+1, 4), 312 ($M^+$, 10), 267 (27), 238 (42), 193 (29), 167 (21), 139 (30), 97 (49), 82 (61), 55 (100); Anal. calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.97. Found: C, 53.63; H, 6.61; N. 8.80.

**3-[3-(2-Hydroxy-ethyl)-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl) propionic acid ethyl ester (5e).** Pale yellow oil; isolated yield: 1.95 g (76%); IR (neat) $\nu_{max}$ ($cm^{-1}$): 3438, 3079, 2969, 1731, 1705, 1651; $^1$H NMR ($CDCl_3$): δ 1.17 (3H, t, *J* = 7.2 Hz, $CH_2CH_3$), 2.70 (2H, t, *J* = 6.0 Hz, O=C$CH_2$), 3.35 (1H, br, *OH*), 3.73 (2H, t, *J* = 5.0 Hz, $HOCH_2CH_2$), 3.94 (2H, t, *J* = 6.0 Hz, $O{=}CCH_2CH_2$), 4.02-4.16 (4H, complex, $HOCH_2$ and $CH_3CH_2$), 5.65 (1H, d, *J* = 7.9 Hz, $H_5$ of uracil), 7.33 (1H, d, *J* = 7.9 Hz, $H_6$ of uracil); $^{13}$C NMR ($CDCl_3$): δ 14.4, 33.2, 37.2, 43.7, 46.5, 61.4, 101.3, 144.5, 152.1, 164.2, 171.7; MS m/z (%): 257 ($M^+$+1, 36), 256 ($M^+$, 2), 213 (44), 157 (19), 139 (17), 97 (55), 82 (100), 55 (75); Anal. calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.74; H, 6.07; N. 10.67.

**3-[3-(4-Nitrobenzyl)-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl]-propionic acid ethyl ester (5f).** Pale yellow crystals, mp 84-86 °C; isolated yield: 2.83 g (82%); IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3080, 2991, 1731, 1713, 1636, 1605, 1491; $^1$H NMR ($CDCl_3$): δ 1.21 (3H, t, *J* = 7.1 Hz, $CH_2CH_3$), 2.74

(2H, t, *J* = 6.1 Hz, O=C*CH*$_2$), 3.98 (2H, t, *J* = 6.1 Hz, O=CCH$_2$*CH*$_2$), 4.09 (2H, q, *J* = 7.1 Hz, CH$_3$*CH*$_2$), 5.15 (2H, s, Ar*CH*$_2$), 5.73 (1H, d, *J* = 8.0 Hz, H$_5$ of uracil), 7.37 (1H, d, *J* = 8.0 Hz, H$_5$ of uracil), 7.58 (2H, d, *J* = 8.8 Hz), 8.12 (2H, d, *J* = 8.8 Hz); $^{13}$C NMR (CDCl$_3$): δ 14.5, 33.3, 43.9, 46.6, 61.5, 101.5, 123.9, 130.1, 144.1, 144.6, 147.7, 151.7, 163.1, 171.6; MS m/z (%): 348 ($M^+$+1, 8), 347 ($M^+$, 36), 302 (14), 273 (15), 170 (40), 124 (13), 97 (56), 82 (61), 55 (100); Anal. calcd for $C_{16}H_{17}N_3O_5$: C, 55.33; H, 4.93; N, 12.10. Found: C, 55.04; H, 5.31; N. 12.34.

**3-(3-Allyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl) propionic acid ethyl ester (5g).** Pale yellow oil; isolated yield: 2.27 g (90%); IR (neat) $\nu_{max}$ (cm$^{-1}$): 3048, 2978, 1735, 1701, 1640; $^1$H NMR (CDCl$_3$): δ 1.18 (3H, t, *J* = 7.1 Hz, CH$_2$*CH*$_3$), 2.70 (2H, d, *J* = 5.9 Hz, O=C*CH*$_2$), 3.93 (2H, t, *J* = 5.9 Hz, O=CCH$_2$*CH*$_2$), 4.09 (2H, q, *J* = 7.1 Hz, CH$_3$*CH*$_2$), 4.46 (2H, d, *J* = 5.8 Hz, H$_2$C=CH*CH*$_2$), 5.09-5.19 (2H, complex, =*CH*$_2$), 5.62 (1H, d, *J* = 7.9 Hz, H$_5$ of uracil), 5.79 (1H, m, H$_2$C=*CH*), 7.27 (1H, d, J = 7.9 Hz, H$_6$ of uracil); $^{13}$C NMR (CDCl$_3$): δ 14.5, 33.4, 43.4, 46.5, 61.4, 101.6, 118.1, 131.9, 143.9, 151.5, 163.1, 171.7; MS m/z (%): 253 ($M^+$+1, 15), 252 ($M^+$, 21), 237 (63), 178 (18), 150 (14), 97 (88), 82 (100), 55 (84); Anal. calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 56.95; H, 6.04; N. 11.43.

**3-(2,4-Dioxo-3-prop-2-ynyl-3,4-dihydro-2*H*-pyrimidin-1-yl) propionic acid ethyl ester (5h).** Pale yellow oil; isolated yield: 2.15g (86 %); IR (neat) $\nu_{max}$ (cm$^{-1}$): 3248, 3071, 2980, 1735, 1701, 1636; $^1$H NMR (CDCl$_3$): δ 1.18 (3H, t, *J* = 7.1 Hz, CH$_2$*CH*$_3$), 2.14 (1H, s), 2.73 (2H, t, *J* = 6.1 Hz, O=C*CH*$_2$), 3.96 (2H, t, J = 6.1 Hz, O=CCH$_2$*CH*$_2$), 4.09 (2H, q, J = 7.1 Hz, CH$_3$*CH*$_2$), 4.60 (2H, s), 5.67 (1H, d, *J* = 8.0 Hz, H$_5$ of uracil), 7.35 (1H, d, *J* = 8.0 Hz, H$_6$ of uracil); $^{13}$C NMR (CDCl$_3$): δ 14.4, 30.5, 33.3, 38.2, 46.5, 61.4, 71.2, 101.3, 144.5, 151.0, 162.3, 171.6; MS m/z (%): 251 ($M^+$+1, 19), 250 ($M^+$, 24), 205 (32), 178 (44), 150 (58), 96 (49), 82 (83), 55 (100); Anal. calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.19. Found: C, 57.87; H, 5.93; N. 11.50.

**3-[3-(3-Chloro-propyl)-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl] propionic acid ethyl ester (5i).** Pale yellow oil; isolated yield: 2.38 g (79 %); IR (neat) $\nu_{max}$ (cm$^{-1}$): 3061, 2970, 1735, 1699, 1658; $^1$H NMR (CDCl$_3$): δ 1.19 (3H, t, *J* = 7.1 Hz, CH$_2$*CH*$_3$), 1.88 (3H, s, *CH*$_3$), 2.02 (2H, m, ClCH$_2$*CH*$_2$), 2.69 (2H, t, *J* = 6.0 Hz, O=C*CH*$_2$), 3.48 (2H, t, *J* = 7.3 Hz, ClCH$_2$CH$_2$*CH*$_2$), 3.96-4.08 (6H, complex, ClCH$_2$, O=CCH$_2$*CH*$_2$ and CH$_3$*CH*$_2$), 7.22 (1H, s, H$_6$ of thymine); $^{13}$C NMR (CDCl$_3$): δ 14.3, 15.2, 30.3, 33.5, 38.4, 41.1, 45.5, 61.2, 109.1, 135.6, 149.2, 163.5, 171.1; MS m/z (%): 303 ($M^+$+1, 10), 302 ($M^+$, 4), 267 (54), 225 (33), 180 (13), 156 (27), 97 (67), 55 (100); Anal. calcd for $C_{13}H_{19}ClN_2O_4$: C, 51.57; H, 6.33; N, 9.25. Found: C, 51.39; H, 5.97; N. 9.58.

**3-[3-(2-Hydroxy-ethyl)-5-methyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl) propionic acid ethyl ester (5j).** Pale yellow oil; isolated yield: 1.68 g (62 %); IR (neat) $\nu_{max}$ (cm$^{-1}$): 3045, 2963, 1733, 1693, 1660; $^1$H NMR (CDCl$_3$): δ 1.15 (3H, t, *J* = 7.1 Hz, CH$_2$*CH*$_3$), 1.90 (3H, s, *CH*$_3$), 2.72 (2H, t, *J* = 6.0 Hz, O=C*CH*$_2$), 3.40 (1H, br, *OH*), 3.68 (2H, t, *J* = 5.1, HOCH$_2$*CH*$_2$), 3.91 (2H, t, *J* = 6.0 Hz, O=CCH$_2$*CH*$_2$), 4.13-4.22 (4H, complex, HO*CH*$_2$ and CH$_3$*CH*$_2$), 7.19 (1H, s, H$_6$ of thymine); $^{13}$C NMR (CDCl$_3$): δ 14.4, 15.3, 33.9, 37.6, 42.1, 45.3, 61.3, 108.8, 134.2, 149.9, 162.9, 171.8; MS m/z (%): 271 ($M^+$+1, 25), 270 ($M^+$, 7), 225 (37), 169 (24), 124 (10), 97 (88),

55 (100); Anal. calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.65; H, 6.93; N. 10.02.

**3-[3-(3-Chloro-propyl)-5-fluoro-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl] propionic acid ethyl ester (5k).** Pale yellow oil; isolated yield: 2.86 g (93 %); IR (neat) $\nu_{max}$ ($cm^{-1}$): 3071, 2981, 1729, 1713, 1667; $^1H$ NMR ($CDCl_3$): δ 1.20 (3H, t, *J* = 7.1 Hz, $CH_2CH_3$), 2.01 (2H, m, $ClCH_2CH_2$), 2.79 (2H, t, *J* = 5.9 Hz, O=C$CH_2$), 3.51 (2H, t, *J* = 7.2 Hz, $ClCH_2CH_2CH_2$), 4.02-4.16 (6H, complex, $ClCH_2$, $O=CCH_2CH_2$ and $CH_3CH_2$), 7.85 (1H, d, *J* = 6.5 Hz, $H_6$ of 5-fluorouracil); $^{13}C$ NMR ($CDCl_3$): δ 14.3, 30.2, 33.8, 38.2, 40.7, 45.5, 61.1, 119.5, 138.7, 148.6, 161.7, 171.2; MS m/z (%): 307 ($M^+$+1, 18), 306 ($M^+$, 6), 271 (68), 229 (42), 205 (12), 128 (19), 97 (81), 55 (100); Anal. calcd for $C_{12}H_{16}ClFN_2O_4$: C, 46.99; H, 5.26; N, 9.13. Found: C, 47.28; H, 4.94; N. 8.85.

**3-[3-(2-Hydroxy-ethyl)-5-fluoro-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl) propionic acid ethyl ester (5l).** Pale yellow oil; isolated yield: 2.05 g (75 %); IR (neat) $\nu_{max}$ ($cm^{-1}$): 3071, 2968, 1734, 1707, 1657; $^1H$ NMR ($CDCl_3$): δ 1.23 (3H, t, *J* = 7.1 Hz, $CH_2CH_3$), 2.81 (2H, t, *J* = 5.8 Hz, O=C$CH_2$), 3.44 (1H, br, *OH*), 3.73 (2H, t, *J* = 5.1 Hz, $HOCH_2CH_2$), 3.96 (2H, t, *J* = 5.8 Hz, $O=CCH_2CH_2$), 4.12-4.23 (4H, complex, $HOCH_2$ and $CH_3CH_2$), 7.91 (1H, d, *J* = 6.5 Hz, $H_6$ of 5-fluorouracil); $^{13}C$ NMR ($CDCl_3$): δ 14.5, 34.1, 38.9, 41.5, 45.4, 61.3, 118.6, 139.4, 148.3, 61.1, 171.4; MS: m/z (%) = 275 ($M^+$+1, 13), 274 ($M^+$, 3), 229 (48), 201 (16), 173 (18), 128 (22), 97 (85), 55 (100); Anal. calcd for $C_{11}H_{15}FN_2O_5$: C, 48.17; H, 5.51; N, 10.21. Found: C, 47.80; H, 5.72; N. 10.49.

**1-{5-[Bis-(4-methoxy-phenyl)-phenyl-methoxymethyl]-3,4-dihydroxy-tetrahydro-furan-2-yl}-3-(3-chloro-propyl)-1*H*-pyrimidine-2,4-dione (7a).** Pale yellow oil; isolated yield: 5.48 g (88 %); IR (neat) $\nu_{max}$ ($cm^{-1}$): 3445, 3062, 2970, 1703, 1651; $^1H$ NMR ($CDCl_3$): δ 2.05 (2H, m, $ClCH_2CH_2$), 3.48-3.54 (4H, complex), 3.75 (6H, s, 2O$CH_3$), 4.01 (2H, t, *J* = 7.0 Hz, Cl$CH_2$), 4.19 (1H, m), 4.30 (1H, m), 4.44 (1H, m), 4.66 (2H, br, 2*OH*), 5.46 (1H, d, *J* = 8.1 Hz, $H_5$ of uracil), 5.89 (1H, d, *J* = 3.0 Hz,), 6.84 (4H, d, *J* = 8.9 Hz,), 7.20-7.30 (6H, complex), 7.36-7.41 (3H, complex), 7.88 (1H, d, *J* = 8.1 Hz, $H_6$ of uracil); $^{13}C$ NMR ($CDCl_3$): δ 30.6, 39.1, 42.6, 55.2, 62.1, 70.1, 75.8, 83.7, 87.0, 90.9, 101.7, 113.3, 127.1, 128.2, 130.1, 135.1, 135.3, 138.2, 144.3, 151.5, 158.7, 162.7; MS m/z (%): 588 ($M^+$-Cl, 2), 546 (2), 536 (4), 518 (6), 491 (3), 436 (4), 303 (26), 283 (31), 241 (14), 215 (10), 188 (7), 107 (42), 82 (100), 77 (71), 55 (63); Anal. calcd for $C_{33}H_{35}N_2O_8$: C, 63.61; H, 5.66; N, 4.50. Found: C, 63.87; H, 5.87; N. 4.22.

**2-[4-(3-{5-[Bis-(4-methoxy-phenyl)-phenyl-methoxymethyl]-3,4-dihydroxy-tetrahydro-furan-2-yl}-2,6-dioxo-3,6-dihydro-2*H*-pyrimidin-1-yl)-butyl]-isoindole-1,3-dione (7b).** IR (KBr) $\nu_{max}$ ($cm^{-1}$): 3447, 3073, 2932, 1771, 1716, 1651; Pale yellow Crystals; mp 122-124 °C; isolated yield: 6.49 g (87 %); $^1H$ NMR ($CDCl_3$): δ 1.62-1.73 (4H, complex), 3.42-3.50 (4H, complex), 3.76 (6H, s, 2O$CH_3$), 3.91 (2H, t, *J* = 7.1 Hz,), 4.21 (1H, m), 4.31 (1H, m), 4.41 (1H, m), 4.60 (2H, br, 2*OH*), 5.44 (1H, d, *J* = 8.0 Hz, $H_5$ of uracil), 5.87 (1H, d, *J* = 3.0 Hz), 6.83 (4H, d, *J* = 9.0 Hz), 7.24-7.29 (6H, complex), 7.35-7.39 (3H, complex), 7.67 (2H, m), 7.80 (2H, m), 7.86 (1H, d, *J* = 8.1 Hz, $H_6$ of uracil); $^{13}C$ NMR ($CDCl_3$): δ 24.9, 25.9, 37.6, 40.5, 62.2, 70.3, 75.8, 83.9, 86.9, 91.2, 101.6, 113.2, 123.2, 127.1, 128.0, 130.1, 132.0, 133.9, 135.1, 135.3, 137.9,

144.3, 151.5, 158.6, 162.6, 168.5; MS m/z (%): 587 ($M^+$-$C_9H_6NO_2$, 1), 546 (3), 518 (5), 491 (1), 444 (30), 436 (6), 338 (12), 303 (36), 242 (5), 202 (20), 146 (45), 133 (34), 107 (55), 82 (100), 55 (48); Anal. calcd for $C_{42}H_{41}N_3O_{10}$: C, 67.46; H, 5.53; N, 5.62. Found: C, 67.82; H, 5.80; N. 5.89.

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